Bioenergetics: The Role of ATP

BIOMEDICAL IMPORTANCE

Bioenergetics, or biochemical thermodynamics, is the study of the energy changes accompanying biochemical reactions. Biologic systems are essentially **isothermic** and use chemical energy to power living processes.How an animal obtains suitable fuel from its food to provide this energy is basic to the understanding of normal nutrition and metabolism. Death from **starvation** occurs when available energy reserves are depleted, and certain forms of malnutrition are associated with energy imbalance **(marasmus).** Thyroid hormones control the rate of energy release (metabolic rate), and disease results when they malfunction. Excess storage of surplus energy causes **obesity,** one of the most common diseases of Western society.

FREE ENERGY IS THE USEFUL ENERGY IN A SYSTEM

Gibbs change in free energy (ΔG) is that portion of the total energy change in a system that is available for doing work—ie, the useful energy, also known as the chemical potential.

Biologic Systems Conform to the General Laws of Thermodynamics

The first law of thermodynamics states that **the total energy of a system, including its surroundings, remains constant.** It implies that within the total system, energy is neither lost nor gained during any change. However, energy may be transferred from one part of the system to another or may be transformed into another form of energy. In living systems, chemical energy may be transformed into heat or into electrical, radiant, or mechanical energy.

The second law of thermodynamics states that **the total entropy of a system must increase if a process is to occur spontaneously. Entropy** is the extent of disorder or randomness of the system and becomes maximum as equilibrium is

approached. Under conditions of constant temperature and pressure, the relationship between the free energy change (ΔG) of a reacting
system and the change in entropy (ΔS) is expressed by the following equation, which combines
the two laws of thermodynamics: $\Delta G = \Delta H - T\Delta S$
where ΔH is the change in **enthalpy** (heat) and T is the absolute temperature. In biochemical reactions, because ΔH is approximately equal to ΔE, the total change in internal energy of the reaction, the above relationship may be expressed in the following way: $\Delta G = \Delta E - T\Delta S$

If ΔG is negative, the reaction proceeds spontaneously with loss of free energy; ie, it is **exergonic.** If, in addition, ΔG is of great magnitude, the reaction goes virtually to completion and is essentially irreversible. On the other hand, if ΔG is positive, the reaction proceeds only if free energy can be gained; ie, it is **endergonic.** If, in addition, the magnitude of ΔG is great, the system is stable, with little or no tendency for a reaction to occur. If ΔG is zero, the system is at equilibrium and no net change takes place. When the reactants are present in concentrations of 1.0 mol/L, ΔG0 is the standard free energy change. For biochemical reactions, a standard state is defined as having a pH of 7.0. The standard free energy change at this standard state is denoted by ΔG0'.

ENDERGONIC PROCESSES PROCEED BY COUPLING TO EXERGONIC PROCESSES

The vital processes—eg, synthetic reactions, muscular contraction, nerve impulse conduction, and active transport—obtain energy by chemical linkage, or **coupling,** to oxidative reactions. In its simplest form, this type of coupling may be represented as shown in **Figure 1**. The conversion of metabolite A to metabolite B occurs with release of free energy and is coupled to another reaction in which free energy is required to convert metabolite C to metabolite D. The terms **exergonic** and **endergonic,** rather than the normal chemical terms "exothermic" and "endothermic," are used to indicate that a process is accompanied by loss or gain, respectively, of free energy in any form, not necessarily as heat. In practice, an endergonic process cannot exist independently, but must be a component of a coupled exergonic–endergonic system where the overall net change is exergonic.

The exergonic reactions are termed **catabolism** (generally, the breakdown or oxidation of fuel molecules), whereas the synthetic reactions that build up substances are termed **anabolism.** The combined catabolic and anabolic processes constitute **metabolism.**

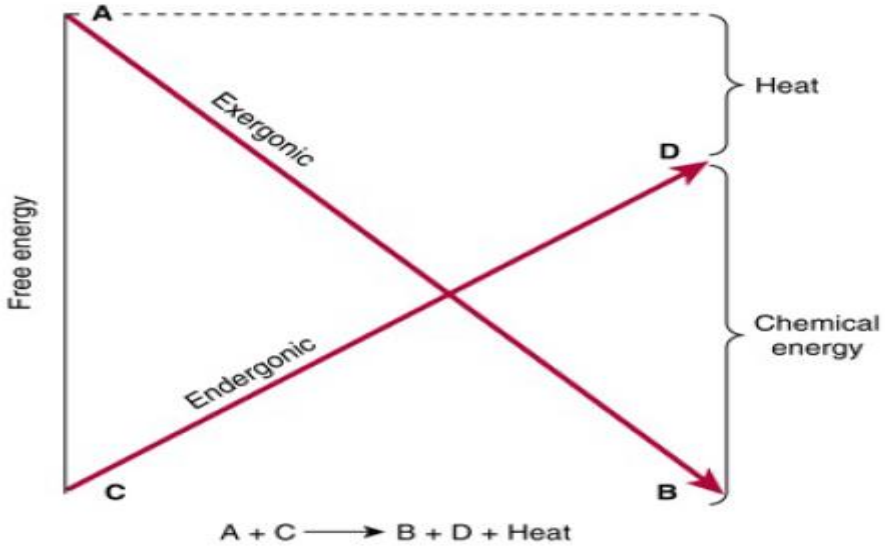


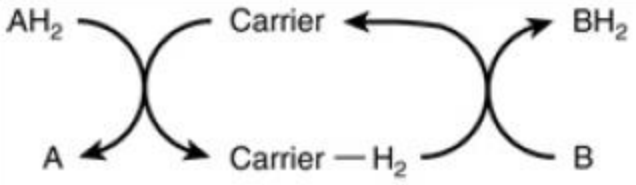
Figure 1: Coupling of an exergonic to an endergonic reaction.

If the reaction shown in **Figure 1** is to go from left to right, then the overall process must be accompanied by loss of free energy as heat. One possible mechanism of coupling
could be envisaged if a common obligatory intermediate (I) took part in both reactions, ie,

$$A + C \rightarrow I \rightarrow B + D$$

Some exergonic and endergonic reactions in biologic systems are coupled in this way. This type of system has a built-in mechanism for biologic control of the rate of oxidative processes since the common obligatory intermediate allows the rate of utilization of the product of the synthetic path (D) to determine by mass action the rate at which A is oxidized. Indeed, these relationships supply a basis for the concept of **respiratory control,** the process that prevents an organism from burning out of control. An extension of the coupling concept is provided by dehydrogenation reactions, which are coupled to hydrogenations by an intermediate carrier (**Figure11- 2**).

Figure 11–2

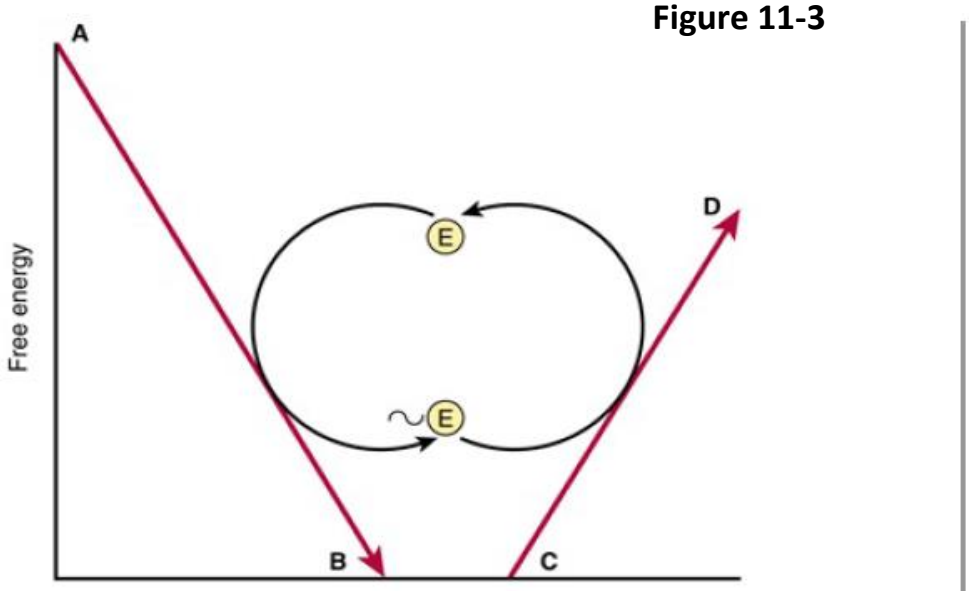


Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA: *Harper's Illustrated Biochemistry, 29th Edition*: www.accessmedicine.com

Coupling of dehydrogenation and hydrogenation reactions by an intermediate carrier.

An alternative method of coupling an exergonic to an endergonic process is to synthesize a compound of high-energy potential in the exergonic reaction and to incorporate this new compound into the endergonic reaction, thus effecting a transference of free energy from the exergonic to the endergonic pathway (**Figure 11–3**). The biologic advantage of this mechanism is that the compound of high potential energy, ~Ⓔ, unlike I in the previous system, need not be structurally related to A, B, C, or D, allowing Ⓔ to serve as a transducer of energy from a wide range of exergonic reactions to an equally wide range of endergonic reactions or processes, such as biosyntheses, muscular contraction, nervous excitation, and active transport. In the living cell, the principal high-energy intermediate or carrier compound (designated ~Ⓔ in **Figure 11–3**) is **adenosine triphosphate (ATP)** (**Figure 11–4**).

Figure 11-3



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Transfer of free energy from an exergonic to an endergonic reaction via a high-energy intermediate compound (~Ⓔ).

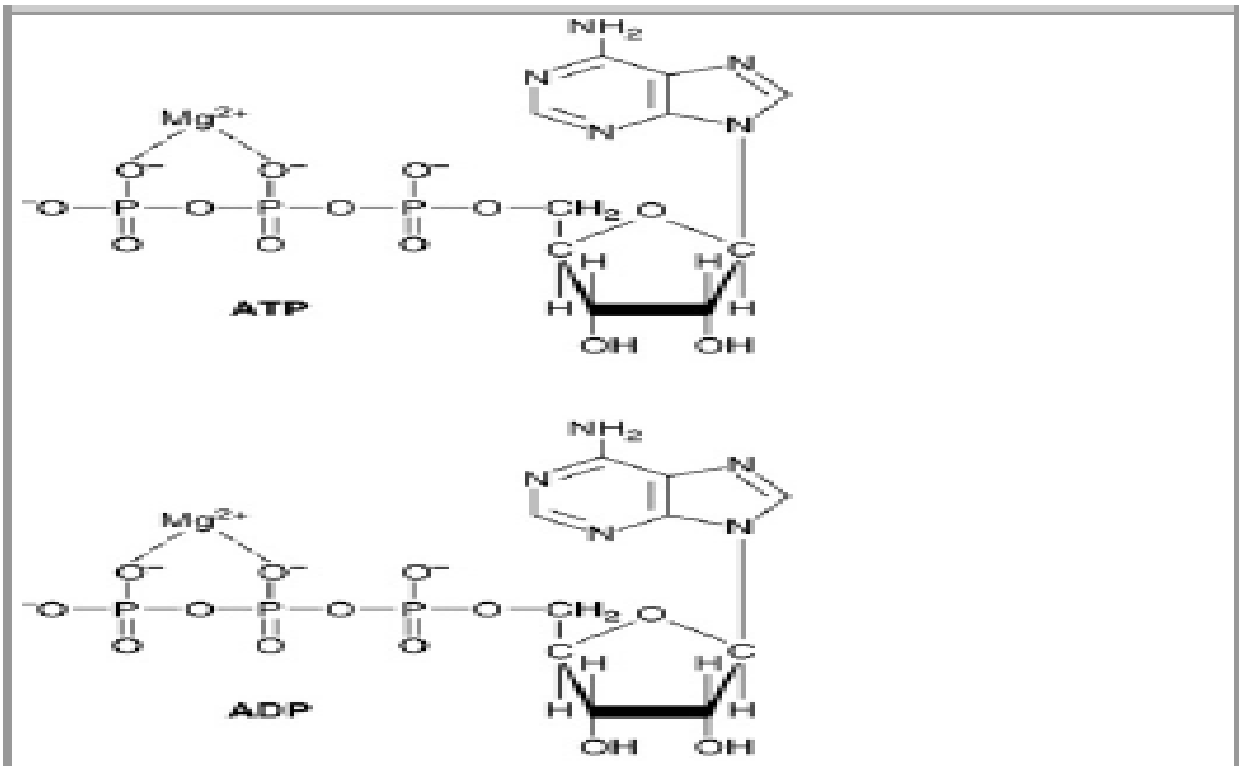


Figure 11-4

HIGH-ENERGY PHOSPHATES PLAY A CENTRAL ROLE IN ENERGY CAPTURE AND TRANSFER

In order to maintain living processes, all organisms must obtain supplies of free energy from their environment. **Autotrophic** organisms utilize simple exergonic processes; eg, the energy of sunlight (green plants), the reaction Fe2+ to Fe3+ (some bacteria). On the other hand, **heterotrophic** organisms obtain free energy by coupling their metabolism to the breakdown of complex organic molecules in their environment. In all these organisms, ATP plays a central role in the transference of free energy from the exergonic to the endergonic processes (**Figure 11–3**). ATP is a nucleoside triphosphate containing adenine, ribose, and three phosphate groups. In its reactions in the cell, it functions as the Mg2+ complex (**Figure 11–4**).

The Intermediate Value for the Free Energy of Hydrolysis of ATP Has Important Bioenergetic Significance

The standard free energy of hydrolysis of a number of biochemically important phosphates is shown in **Table 11–1**. An estimate of the comparative tendency of each of the phosphate groups to transfer to a suitable acceptor may be obtained from the Δ*G*0' of hydrolysis at 37°C. The value for the hydrolysis of the terminal phosphate of ATP divides the list into two groups. **Low-energy phosphates,** exemplified by the ester phosphates found in the intermediates of glycolysis, have *G*0' values smaller than that of ATP, while in **high-energy phosphates** the value is higher than that of ATP. The components of this latter group, including ATP, are usually anhydrides (eg, the 1-phosphate of 1,3-bisphosphoglycerate), enolphosphates (eg, phosphoenolpyruvate), and phosphoguanidines (eg, creatine phosphate, arginine phosphate).

Table 11–1 Standard Free Energy of Hydrolysis of Some Organophosphates of Biochemical Importance

	$-\Delta G^{0'}$	
Compound	**kJ/mol**	**kcal/mol**
Phosphoenolpyruvate	-61.9	-14.8
Carbamoyl phosphate	-51.4	-12.3
1,3-Bisphosphoglycerate (to 3-phosphoglycerate)	-49.3	-11.8
Creatine phosphate	-43.1	-10.3
ATP $\rightarrow$ AMP + PPi	-32.2	-7.7
ATP $\rightarrow$ ADP + P_i	-30.5	-7.3
Glucose 1-phosphate	-20.9	-5.0
PPi	-19.2	-4.6
Fructose 6-phosphate	-15.9	-3.8
Glucose 6-phosphate	-13.8	-3.3
Glycerol 3-phosphate	-9.2	-2.2

The symbol ~Ⓟ indicates that the group attached to the bond, on transfer to an appropriate acceptor, results in transfer of the larger quantity of free energy. For this reason, the term **group transfer potential,** rather than "high-energy bond," is

preferred by some. Thus, ATP contains two high-energy phosphate groups and ADP contains one, whereas the phosphate in AMP (adenosine monophosphate) is of the low-energy type since it is a normal ester link (**Figure 11–5**).

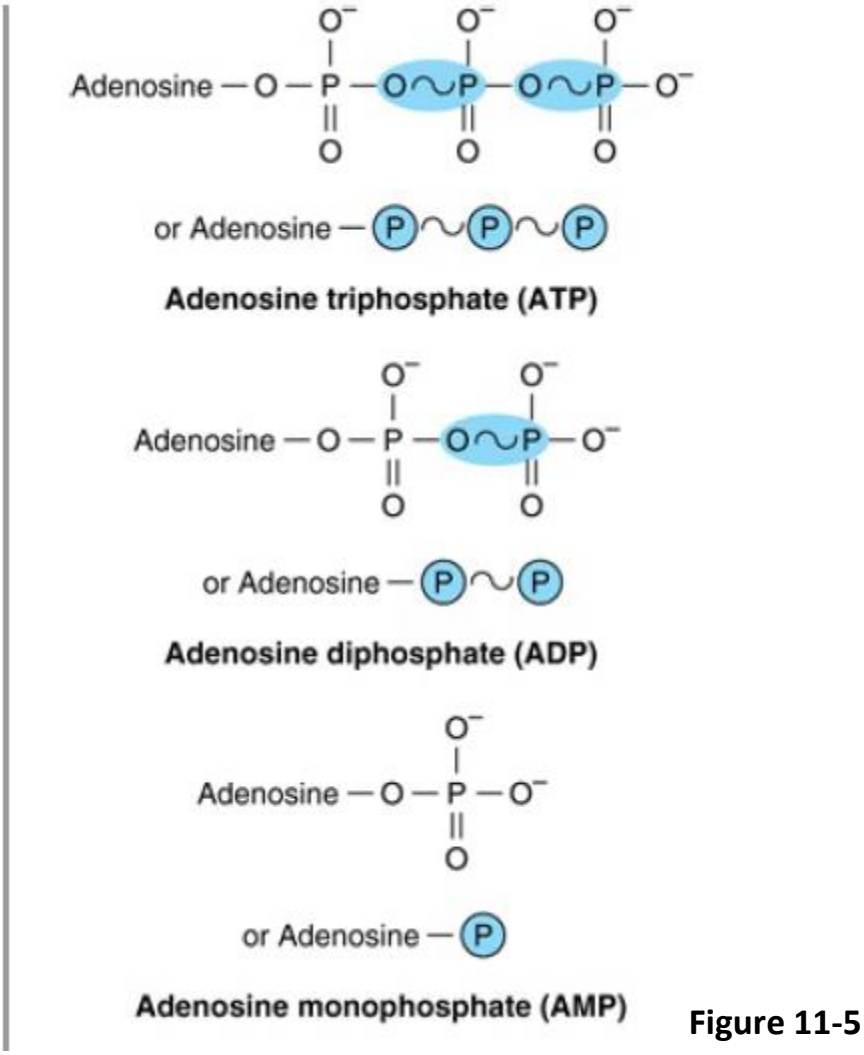


Figure 11-5

The intermediate position of ATP allows it to play an important role in energy transfer. The high free-energy change on hydrolysis of ATP is due to relief of charge repulsion of adjacent negatively charged oxygen atoms and to stabilization of the reaction products, especially phosphate, as resonance hybrids (**Figure 11–6**). Other "high-energy compounds" are thiol esters involving coenzyme A (eg, acetyl-CoA), acyl carrier protein, amino acid esters involved in protein synthesis, *S*-adenosylmethionine (active methionine), UDPGlc (uridine diphosphate glucose), and PRPP (5-phosphoribosyl-1-pyrophosphate).

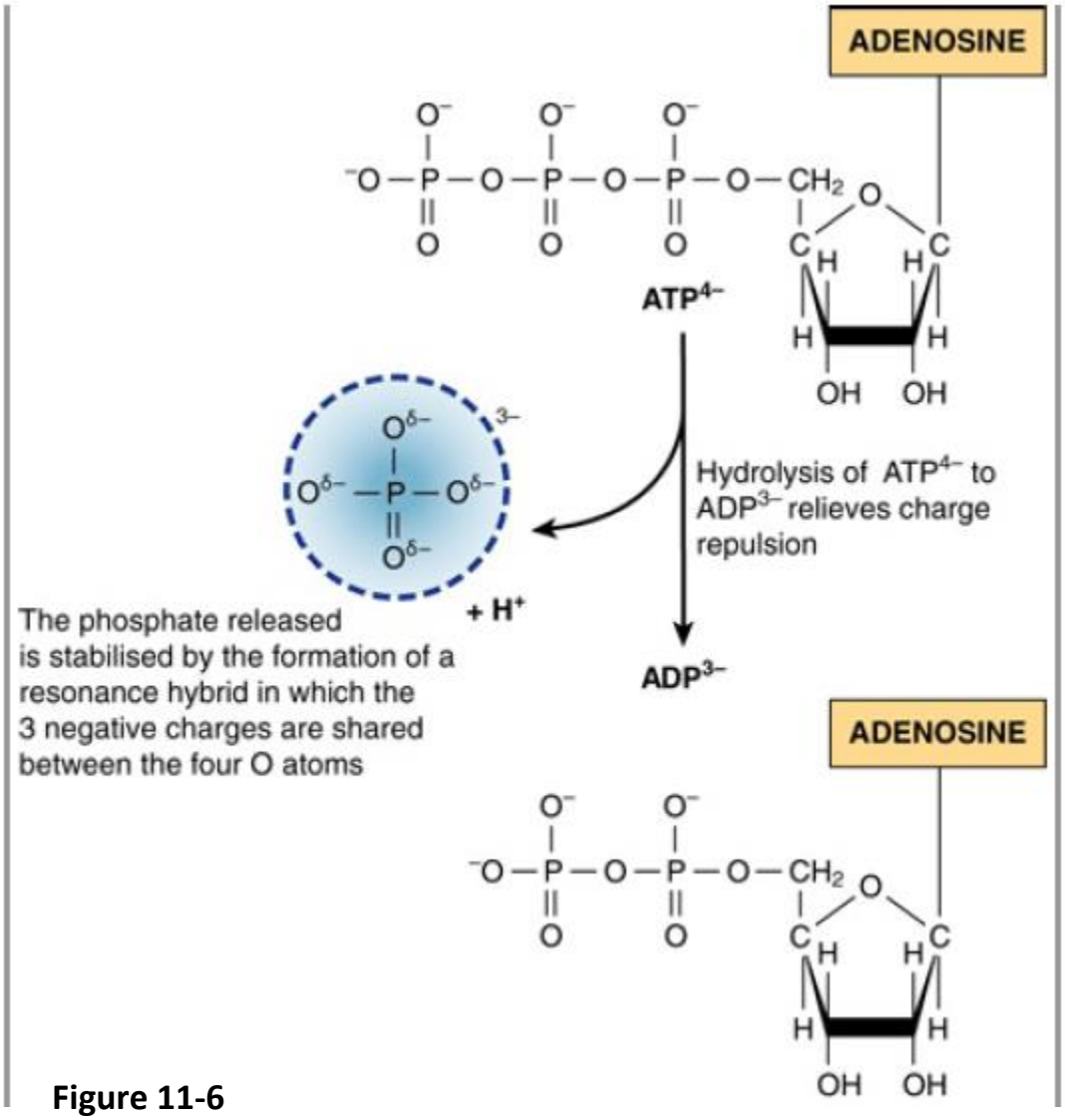
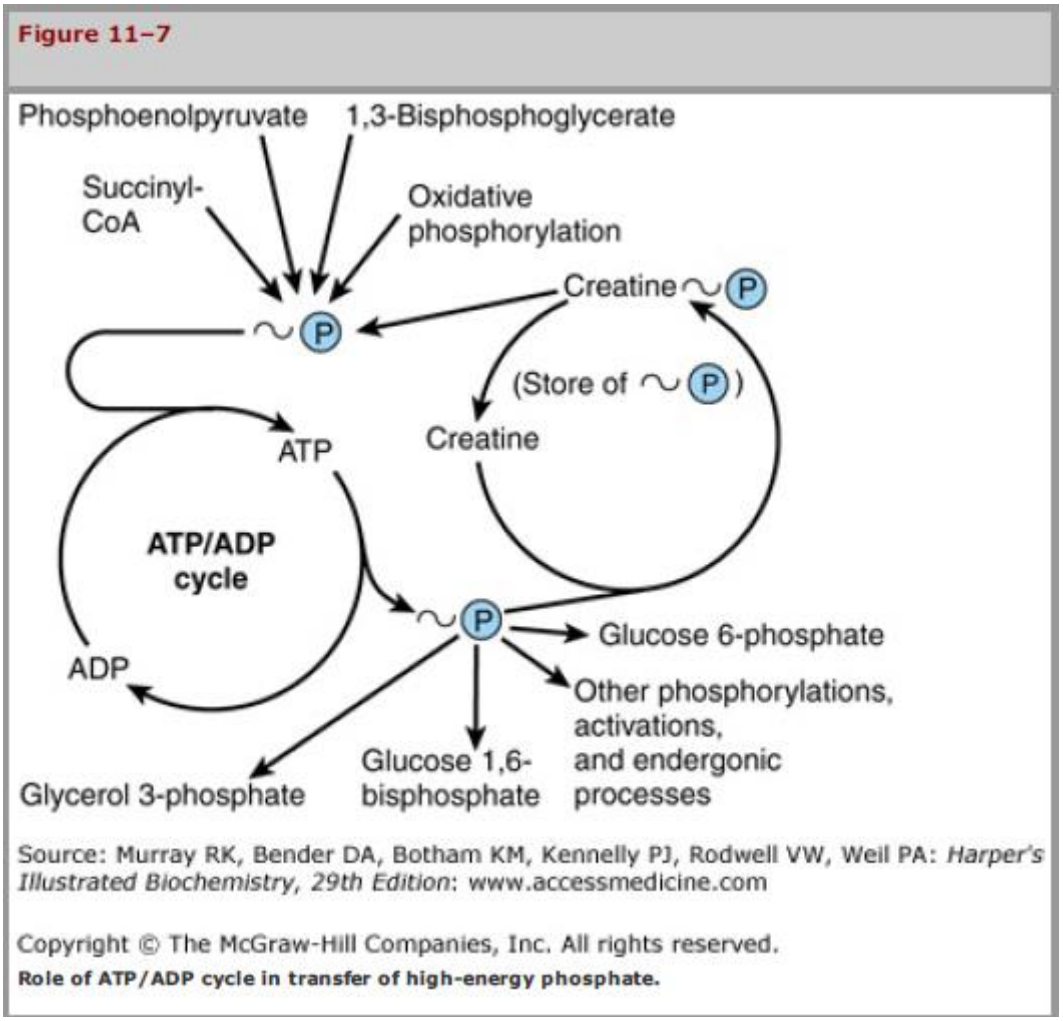


Figure 11-6

HIGH-ENERGY PHOSPHATES ACT AS THE "ENERGY CURRENCY" OF THE CELL

ATP is able to act as a donor of high-energy phosphate to form those compounds below it in **Table 11–1**. Likewise, with the necessary enzymes, ADP can accept high-energy phosphate to form ATP from those compounds above ATP in the table. In effect, an **ATP/ADP cycle** connects those processes that generate ~Ⓟ to those processes that utilize ~Ⓟ (**Figure 11–7**), continuously consuming and regenerating ATP. This occurs at a very rapid rate since the total ATP/ADP pool is extremely small and sufficient to maintain an active tissue for only a few seconds.



There are three major sources of ~Ⓟ taking part in **energy conservation** or **energy capture:**

1. **Oxidative phosphorylation.** The greatest quantitative source of ~Ⓟ in aerobic organisms. Free energy comes from respiratory chain oxidation using molecular O2 within mitochondria .

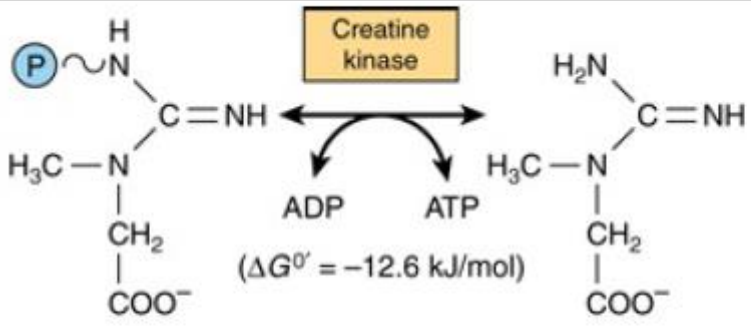
2. **Glycolysis.** A net formation of two ~ results from the formation of lactate from one molecule of glucose, generated in two reactions catalyzed by phosphoglycerate kinase and pyruvate kinase, respectively .

3. **The citric acid cycle.** One ~ is generated directly in the cycle at the succinate thiokinase step .

Phosphagens act as storage forms of high-energy phosphate and include creatine phosphate, which occurs in vertebrate skeletal muscle, heart, spermatozoa, and brain, and arginine phosphate, which occurs in invertebrate muscle. When ATP is rapidly being utilized as a source of energy for muscular contraction, phosphagens

permit its concentrations to be maintained, but when the ATP/ADP ratio is high, their concentration can increase to act as a store of high-energy phosphate (**Figure 11–8**).

Figure 11–8



Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA: *Harper's Illustrated Biochemistry, 29th Edition*: www.accessmedicine.com

Transfer of high-energy phosphate between ATP and creatine.

ATP Allows the Coupling of Thermodynamically Unfavorable Reactions to Favorable Ones

The phosphorylation of glucose to glucose 6-phosphate, the first reaction of glycolysis (**Figure 18–2**), is highly endergonic and cannot proceed under physiologic conditions:

$$\text{Glucose} + P_i \rightarrow \text{Glucose 6-phosphate} + H_2O \qquad (1)$$

$$(\Delta G^{0'} = +13.8 \text{ kJ/mol})$$

To take place, the reaction must be coupled with another—more exergonic—reaction such as the hydrolysis of the terminal phosphate of ATP.

$$\text{ATP} \rightarrow \text{ADP} + P_i \ (\Delta G^{0'} = -30.5 \text{ kJ/mol}) \qquad (2)$$

When (1) and (2) are coupled in a reaction catalyzed by hexokinase, phosphorylation of glucose readily proceeds in a highly exergonic reaction that

under physiologic conditions is irreversible. Many "activation" reactions follow this pattern.

Adenylyl Kinase (Myokinase) Interconverts Adenine Nucleotides

This enzyme is present in most cells. It catalyzes the following reaction:

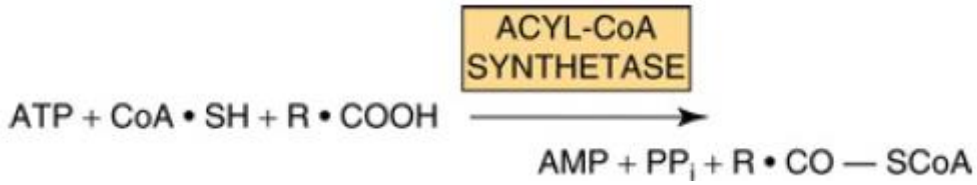
This allows:

1. High-energy phosphate in ADP to be used in the synthesis of ATP.
2. AMP, formed as a consequence of several activating reactions involving ATP, to be recovered by rephosphorylation to ADP.
3. AMP to increase in concentration when ATP becomes depleted and act as a metabolic (allosteric) signal to increase the rate of catabolic reactions, which in turn lead to the

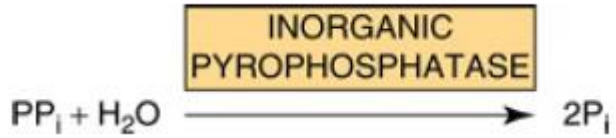
generation of more ATP .

When ATP Forms AMP, Inorganic Pyrophosphate (PPi) Is Produced

ATP can also be hydrolyzed directly to AMP, with the release of PP*i* (**Table 11–1**). This occurs, for example, in the activation of long-chain fatty acids .



This reaction is accompanied by loss of free energy as heat, which ensures that the activation reaction will go to the right and is further aided by the hydrolytic splitting of PP*i*, catalyzed by **inorganic pyrophosphatase,** a reaction that itself has a large *G*0' of –19.2 kJ/mol. Note that activations via the pyrophosphate pathway result in the loss of two ~ rather than one, as occurs when ADP and P*i* are formed.



A combination of the above reactions makes it possible for phosphate to be recycled and the adenine nucleotides to interchange (**Figure 11–9**).

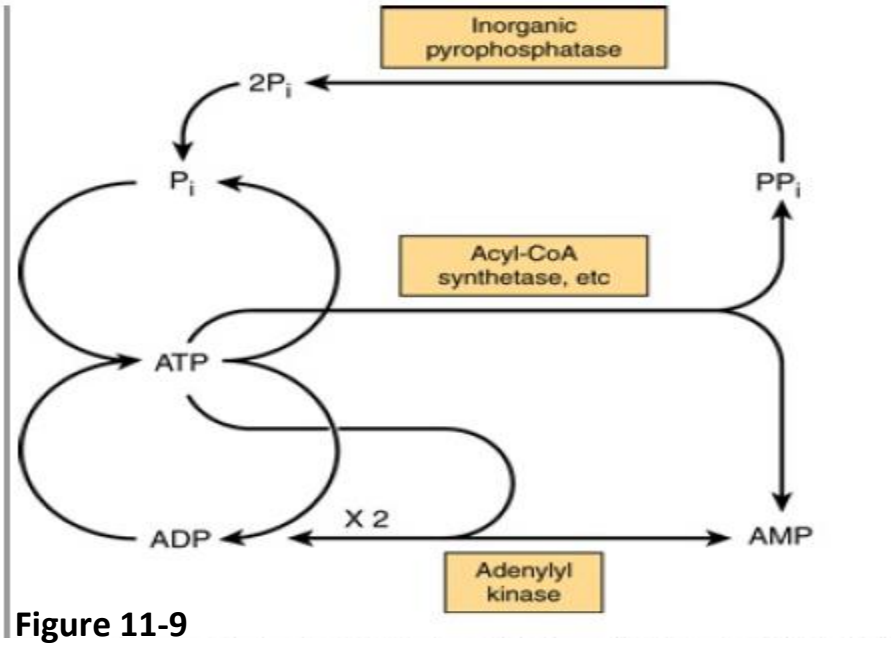
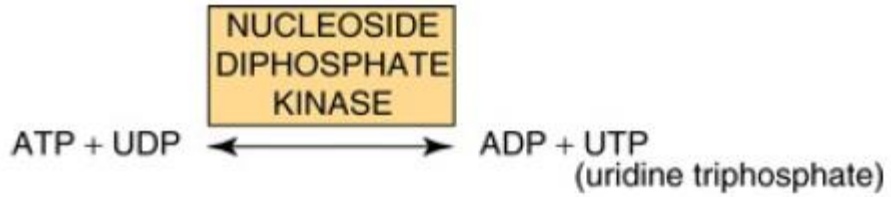


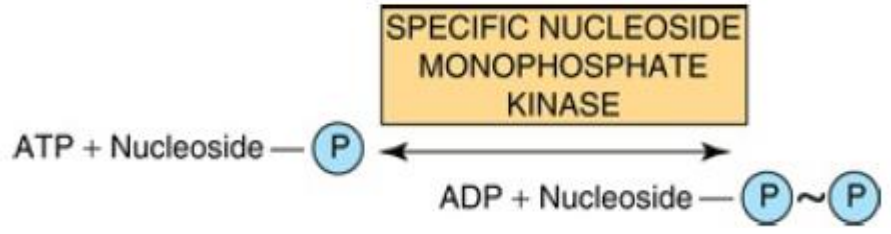
Figure 11-9

Other Nucleoside Triphosphates Participate in the Transfer of High-Energy Phosphate

By means of the enzyme **nucleoside diphosphate kinase,** UTP, GTP, and CTP can be synthesized from their diphosphates, eg, UDP reacts with ATP to form UTP.



All of these triphosphates take part in phosphorylations in the cell. Similarly, specific nucleoside monophosphate kinases catalyze the formation of nucleoside diphosphates from the corresponding monophosphates.



Thus, adenylyl kinase is a specialized monophosphate kinase.

BIOSYNTHESIS OF FATTY ACIDS

BIOMEDICAL IMPORTANCE

Fatty acids are synthesized by an **extramitochondrial system,** which is responsible for the complete synthesis of palmitate from acetyl-CoA in the cytosol. In most mammals, glucose is the primary substrate for lipogenesis, but in ruminants it is acetate, the main fuel molecule produced by the diet. Critical diseases of the pathway have not been reported in humans.

However, inhibition of lipogenesis occurs in type 1 (insulin-dependent) **diabetes mellitus,** and variations in the activity of the process affect the nature and extent of **obesity.**

Unsaturated fatty acids in phospholipids of the cell membrane are important in maintaining membrane fluidity. A high ratio of polyunsaturated fatty acids to saturated fatty acids (P:S ratio) in the diet is considered to be beneficial in preventing coronary heart disease. Animal tissues have limited capacity for desaturating fatty acids, and require certain dietary polyunsaturated fatty acids derived from plants. These **essential fatty acids** are used to form eicosanoic (C20) fatty acids, which give rise to the **eicosanoids** prostaglandins, thromboxanes, leukotrienes, and lipoxins. Prostaglandins mediate **inflammation, pain,** and induce **sleep** and also regulate **blood coagulation** and **reproduction. Nonsteroidal anti-inflammatory drugs (NSAIDs)** such as **aspirin and ibuprofen** act by inhibiting prostaglandin synthesis. Leukotrienes have muscle contractant and chemotactic properties and are important in allergic reactions and inflammation.

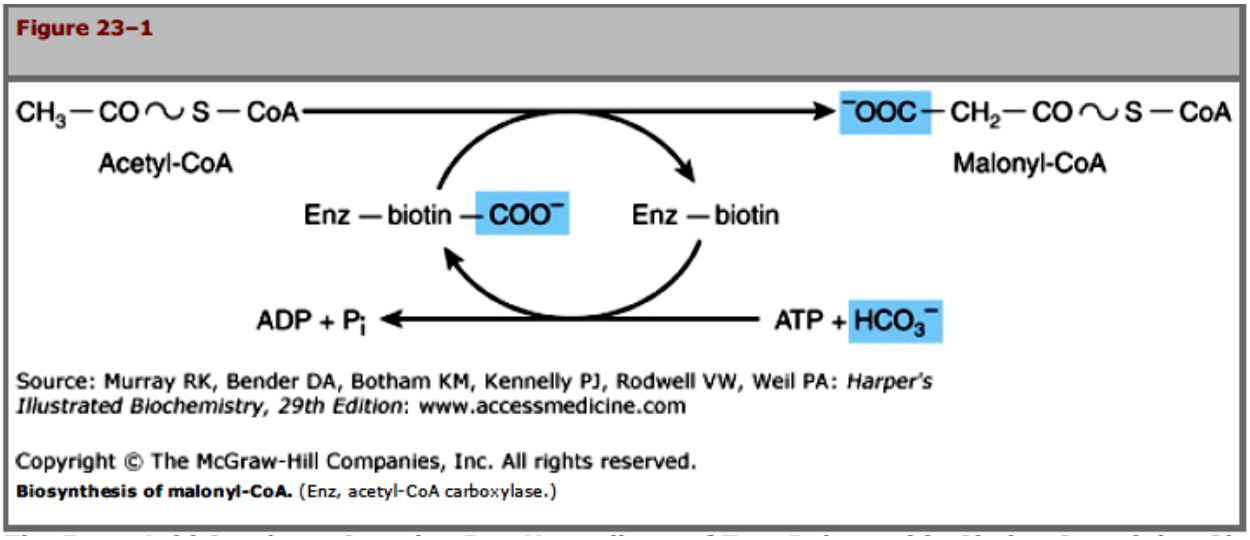
THE MAIN PATHWAY FOR DE NOVO SYNTHESIS OF FATTY ACIDS (LIPOGENESIS) OCCURS IN THE CYTOSOL

This system is present in many tissues, including liver, kidney, brain, lung, mammary gland, and adipose tissue. Its cofactor requirements include NADPH, ATP, Mn^{2+}, biotin, and HCO_3^- (as a source of CO_2). **Acetyl-CoA** is the immediate substrate, and **free palmitate** is the end product.

Production of Malonyl-CoA Is the Initial & Controlling Step in Fatty Acid Synthesis

Bicarbonate as a source of CO_2 is required in the initial reaction for the carboxylation of acetyl-CoA to **malonyl-CoA** in the presence of ATP and **acetyl-**

CoA carboxylase. Acetyl-CoA carboxylase has a requirement for the B vitamin **biotin** (Figure 23–1). The enzyme is a **multienzyme protein** containing a variable number of identical subunits, each containing biotin, biotin carboxylase, biotin carboxyl carrier protein, and transcarboxylase, as well as a regulatory allosteric site. The reaction takes place in two steps: (1) carboxylation of biotin involving ATP and (2) transfer of the carboxyl group to acetyl-CoA to form malonyl-CoA.



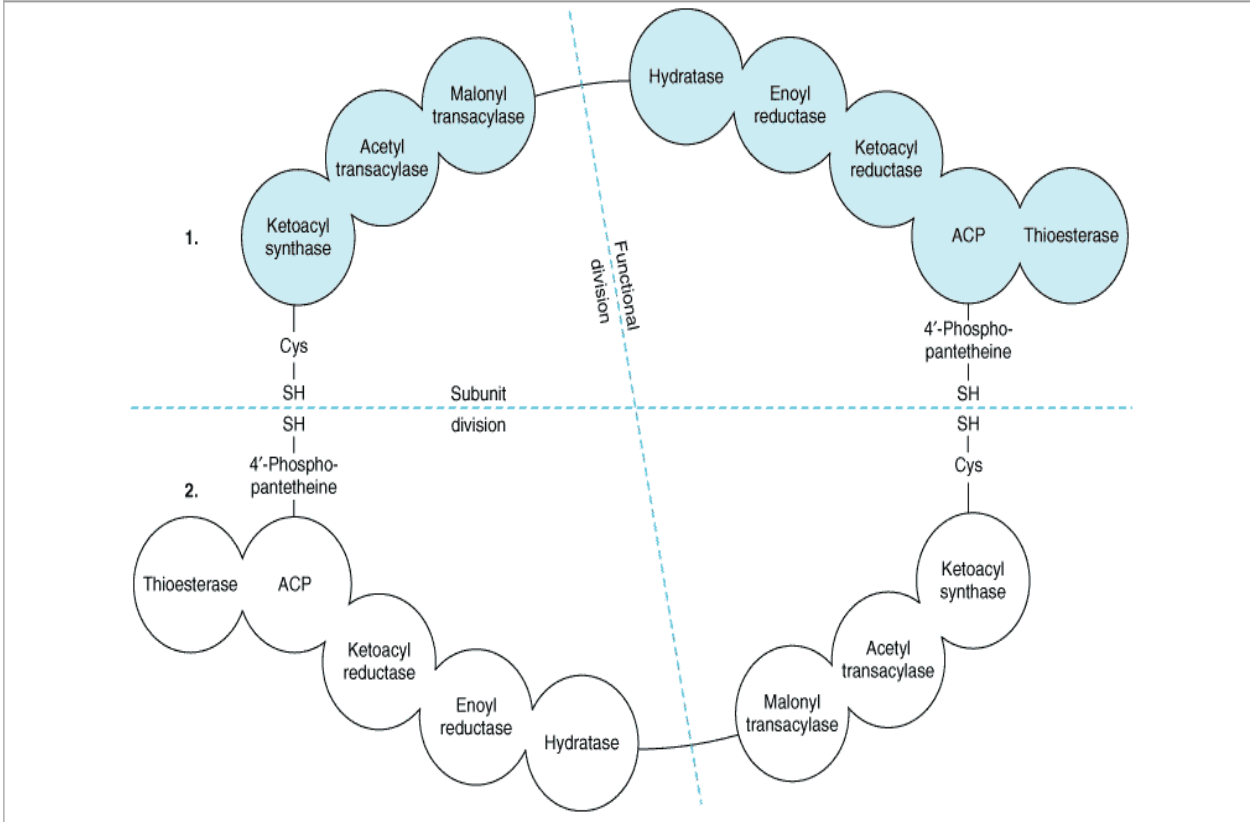
The Fatty Acid Synthase Complex Is a Polypeptide Containing Seven Enzyme Activities

In bacteria and plants, the individual enzymes of the **fatty acid synthase** system are separate, and the acyl radicals are found in combination with a protein called the **acyl carrier protein (ACP).** However, in yeast, mammals, and birds, the synthase system is a multienzyme polypeptide complex that incorporates ACP, which takes over the role of CoA. It contains the vitamin **pantothenic acid** in the form of 4'-phosphopantetheine . The use of one multienzyme functional unit has the advantages of achieving the effect of compartmentalization of the process within the cell without the erection of permeability barriers, and synthesis of all enzymes in the complex is coordinated since it is encoded by a single gene.

In mammals, the fatty acid synthase complex is a dimer comprising two identical monomers, each containing all seven enzyme activities of fatty acid synthase on one polypeptide chain (Figure 23–2). Initially, a priming molecule of acetyl-CoA combines with a cysteine —SH group catalyzed by **acetyl transacylase** (Figure 23–3, reaction 1a). Malonyl-CoA combines with the adjacent —SH on the 4'-phosphopantetheine of ACP of the other monomer, catalyzed by **malonyl**

transacylase (reaction 1b), to form **acetyl (acyl)-malonyl enzyme.** The acetyl group attacks the methylene group of the malonyl residue, catalyzed by **3-ketoacyl synthase,** and liberates CO_2, forming 3-ketoacyl enzyme (acetoacetyl enzyme) (reaction 2), freeing the cysteine —SH group. Decarboxylation allows the reaction to go to completion, pulling the whole sequence of reactions in the forward direction. The 3-ketoacyl group is reduced, dehydrated, and reduced again (reactions 3, 4, 5) to form the corresponding saturated acyl-S-enzyme. A new malonyl-CoA molecule combines with the —SH of 4'-phosphopantetheine, displacing the saturated acyl residue onto the free cysteine —SH group. The sequence of reactions is repeated six more times until a saturated 16-carbon acyl radical (palmityl) has been assembled. It is liberated from the enzyme complex by the activity of a seventh enzyme in the complex, **thioesterase** (deacylase). The free palmitate must be activated to acyl-CoA before it can proceed via any other metabolic pathway. Its usual fate is esterification into acylglycerols, chain elongation or desaturation, or esterification to cholesteryl ester. In mammary gland, there is a separate thioesterase specific for acyl residues of C_8, C_{10}, or C_{12}, which are subsequently found in milk lipids.

Figure 23–2.



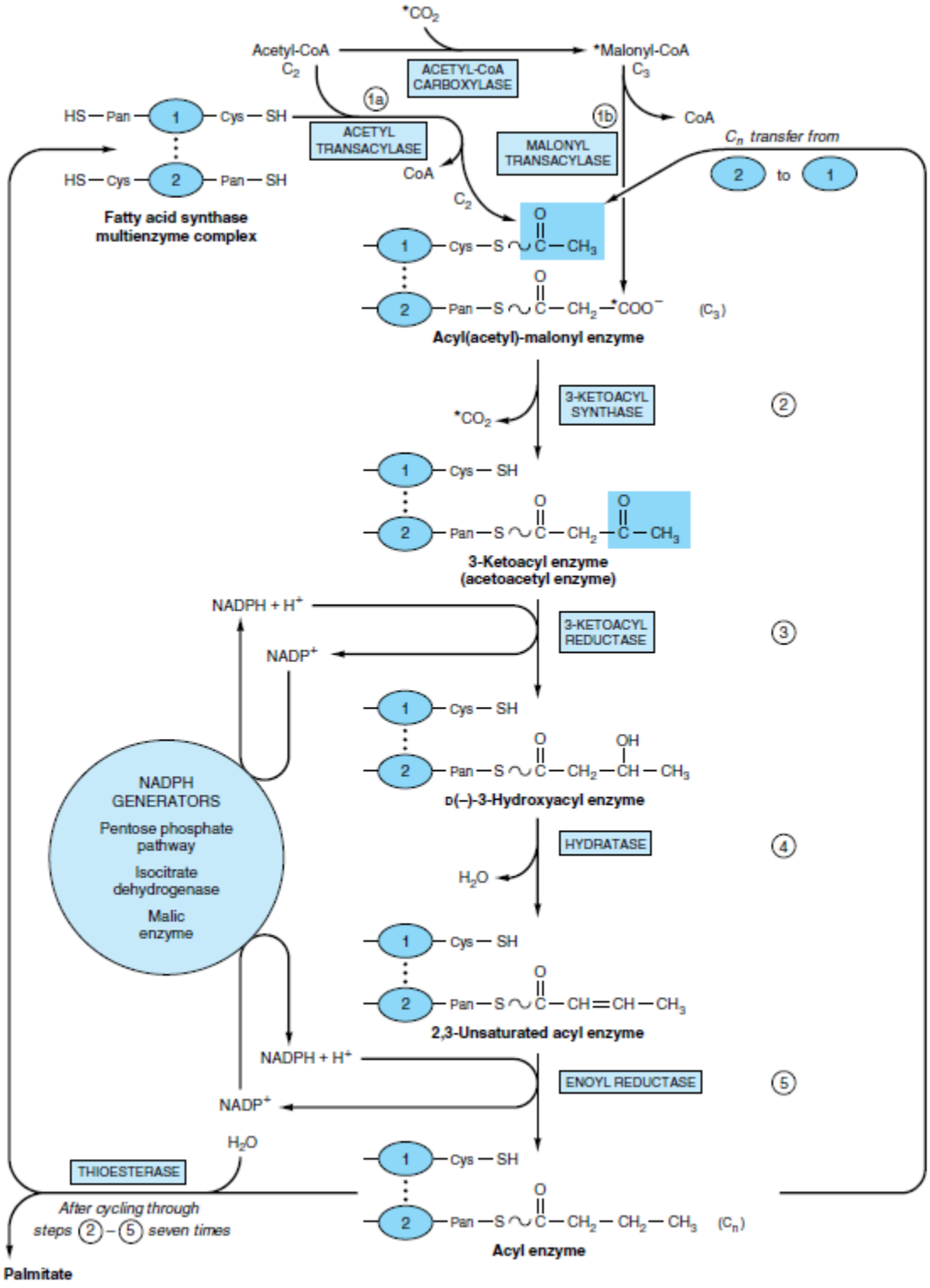

*CO2
Acetyl-CoA
C2
*Malonyl-CoA
C3
ACETYL-CoA CARBOXYLASE
1a
1b
CoA
ACETYL TRANSACYLASE
MALONYL TRANSACYLASE
Cn transfer from
2 to 1
HS — Pan — 1 — Cys — SH
HS — Cys — 2 — Pan — SH
Fatty acid synthase multienzyme complex
Cys — S — C — CH3
Pan — S — C — CH2 — *COO− (C3)
Acyl(acetyl)-malonyl enzyme
*CO2
3-KETOACYL SYNTHASE
2
Cys — SH
Pan — S — C — CH2 — C — CH3
3-Ketoacyl enzyme (acetoacetyl enzyme)
NADPH + H+
NADP+
3-KETOACYL REDUCTASE
3
OH
Pan — S — C — CH2 — CH — CH3
D(−)-3-Hydroxyacyl enzyme
NADPH GENERATORS
Pentose phosphate pathway
Isocitrate dehydrogenase
Malic enzyme
H2O
HYDRATASE
4
Pan — S — C — CH = CH — CH3
2,3-Unsaturated acyl enzyme
ENOYL REDUCTASE
5
THIOESTERASE
Pan — S — C — CH2 — CH2 — CH3 (Cn)
Acyl enzyme
After cycling through steps 2 – 5 seven times
Palmitate
KEY: 1, 2, individual monomers of fatty acid synthase

Figure 23-3.

The equation for the overall synthesis of palmitate from acetyl-CoA and malonyl-CoA is

$$CH_3CO—S—CoA + 7HOOCCHCO—S—CoA + 14NADPH + 14H^+ \rightarrow CH_3(CH_2)_{14}COOH + 7CO_2 + 6H_2O + 8CoA—SH + 14NADP^+$$

The acetyl-CoA used as a primer forms carbon atoms 15 and 16 of palmitate. The addition of all the subsequent C2 units is via malonyl-CoA. Propionyl CoA acts as primer for the synthesis of long-chain fatty acids having an odd number of carbon atoms, found particularly in ruminant fat and milk.

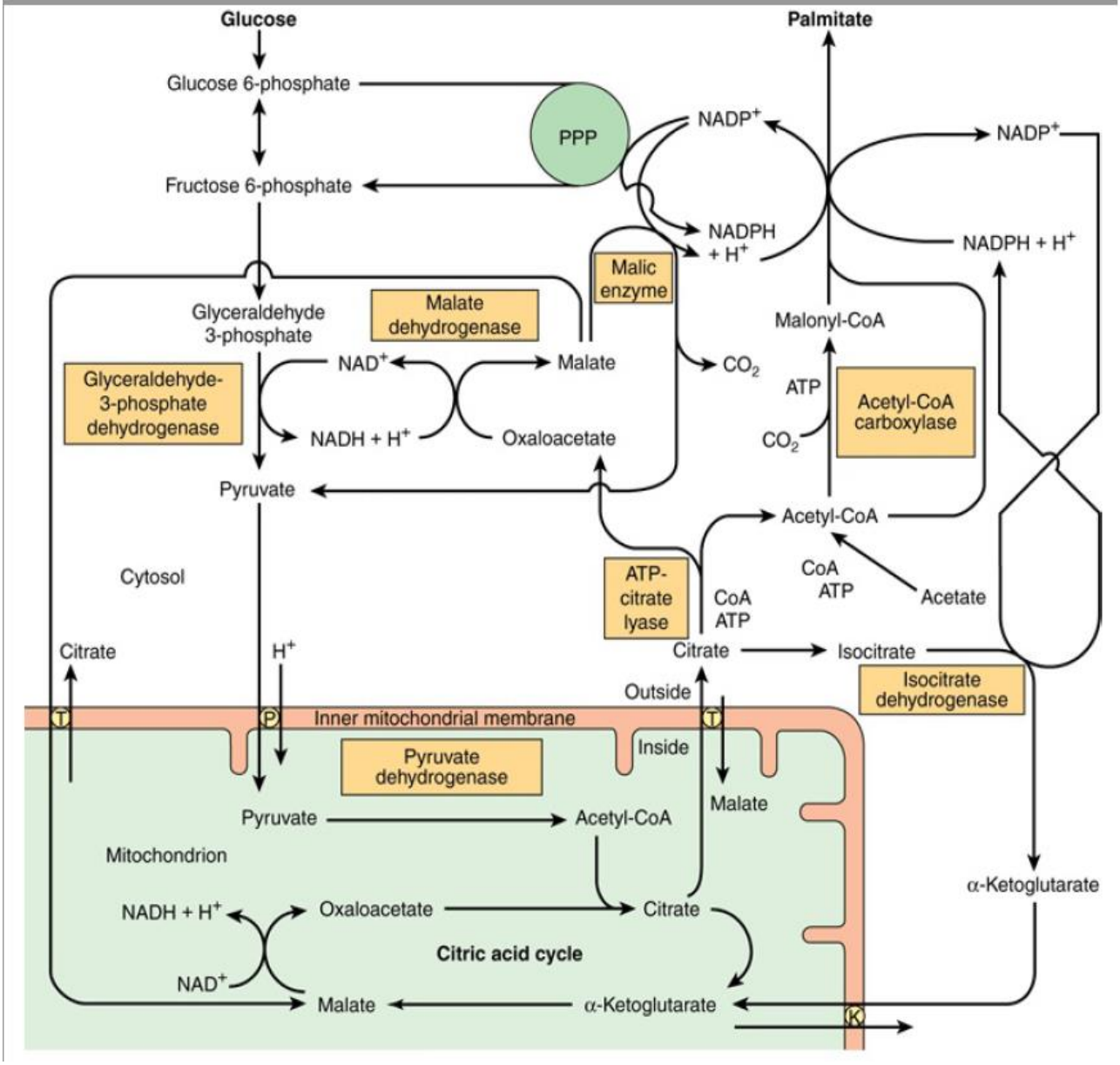
The Main Source of NADPH for Lipogenesis Is the Pentose Phosphate Pathway

NADPH is involved as donor of reducing equivalents in both the reduction of the 3-ketoacyl and of the 2,3-unsaturated acyl derivatives (Figure 23–3, reactions 3 and 5). The oxidative reactions of the pentose phosphate pathway (see Chapter 21) are the chief source of the hydrogen required for the reductive synthesis of fatty acids. Significantly, tissues specializing in active lipogenesis—ie, liver, adipose tissue, and the lactating mammary gland—also possess an active pentose phosphate pathway. Moreover, both metabolic pathways are found in the cytosol of the cell; so, there are no membranes or permeability barriers against the transfer of NADPH. Other sources of NADPH include the reaction that converts malate to pyruvate catalyzed by the **"malic enzyme"** (NADP malate dehydrogenase) (Figure 23–4) and the extramitochondrial **isocitrate dehydrogenase** reaction (probably not a substantial source, except in ruminants).

Acetyl-CoA Is the Principal Building Block of Fatty Acids

Acetyl-CoA is formed from glucose via the oxidation of pyruvate within the mitochondria. However, it does not diffuse readily into the extramitochondrial cytosol, the principal site of fatty acid synthesis. Citrate, formed after condensation of acetyl-CoA with oxaloacetate in the citric acid cycle within mitochondria, is translocated into the extramitochondrial compartment via the tricarboxylate transporter, where in the presence of CoA and ATP, it undergoes cleavage to acetyl-CoA and oxaloacetate catalyzed by **ATP-citratlyase,** which increases in activity in the well-fed state. The acetyl-CoA is then available for malonyl-CoA formation and synthesis to palmitate (Figure 23–4). The resulting oxaloacetate can form malate via NADH-linked malate dehydrogenase, followed by the generation of NADPH via the malic enzyme. The NADPH becomes available

Figure 23–4



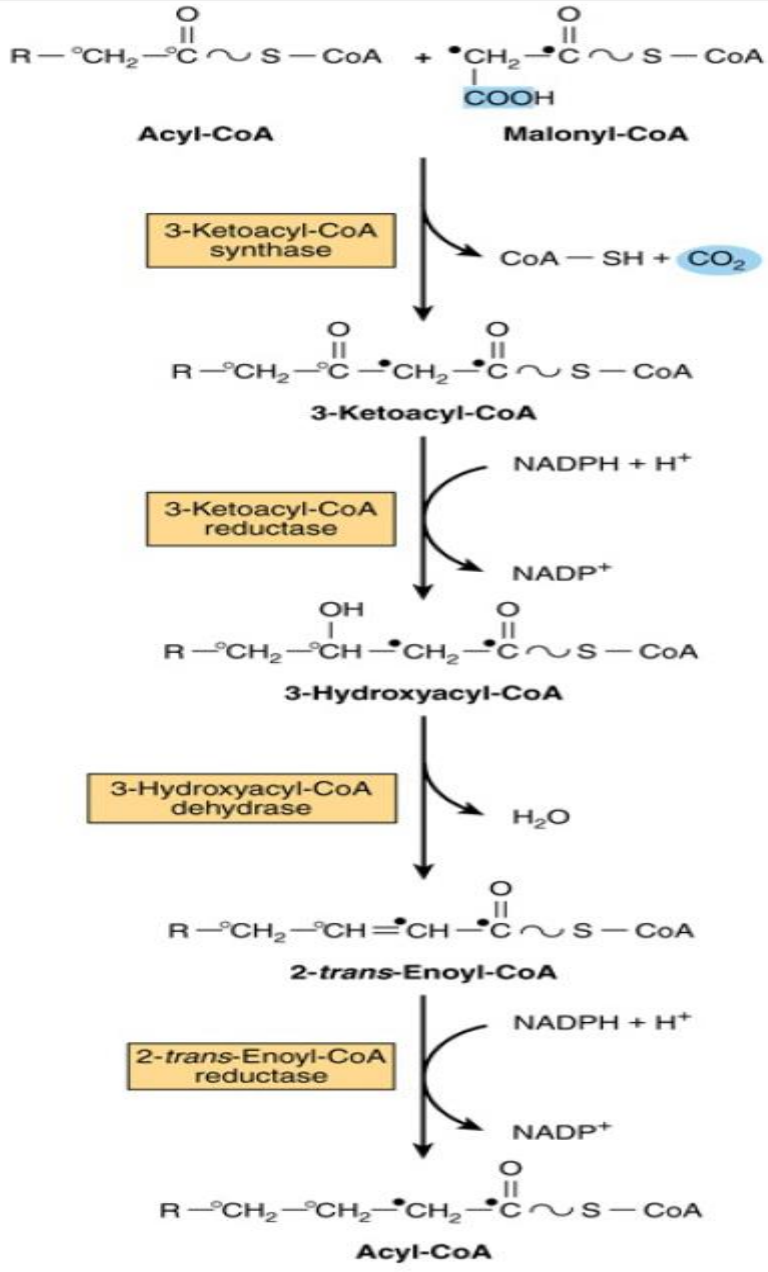
for lipogenesis, and the pyruvate can be used to regenerate acetyl-CoA after transport into the mitochondrion. This pathway is a means of transferring reducing equivalents from extramitochondrial NADH to NADP. Alternatively, malate itself can be transported into the mitochondrion, where it is able to re-form oxaloacetate. Note that the citrate (tricarboxylate) transporter in the mitochondrial membrane requires malate to exchange with citrate (see Figure 13–10). There is little ATP-citrate lyase or malic enzyme in ruminants, probably because in these species acetate (derived from carbohydrate digestion in the rumen and activated to acetyl-CoA extramitochondrially) is the main source of acetyl-CoA.

BIOSYNTHESIS OF FATTY ACIDS

Elongation of Fatty Acid Chains Occurs in the Endoplasmic Reticulum

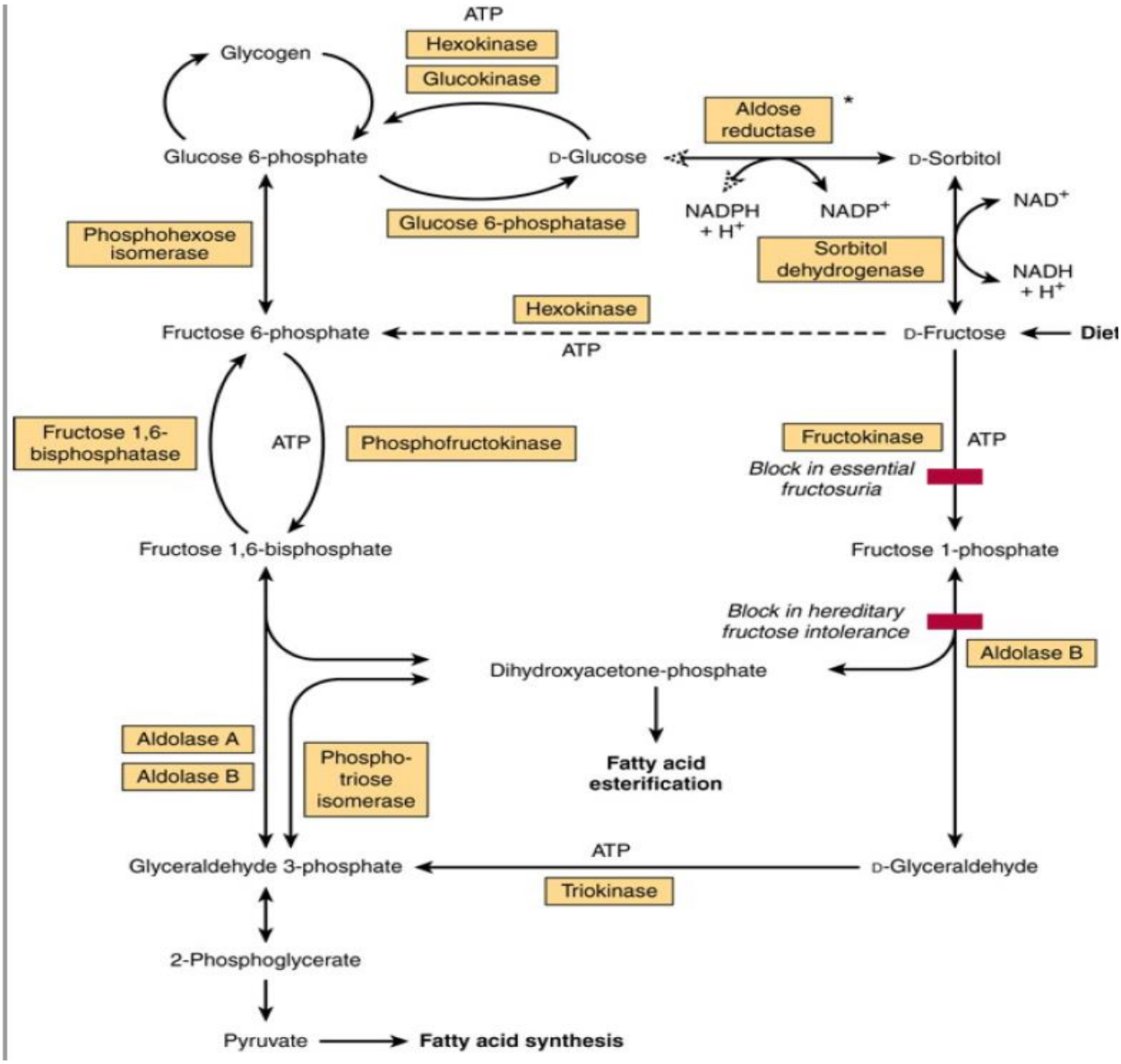
This pathway (**the "microsomal system"**) elongates saturated and unsaturated fatty acyl-CoAs (from C10 upward) by two carbons, using malonyl-CoA as the acetyl donor and NADPH as the reductant, and is catalyzed by the microsomal **fatty acid elongase** system of enzymes (Figure 23–5). Elongation of stearyl-CoA in brain increases rapidly during myelination in order to provide C22 and C24 fatty acids for sphingolipids.

Figure 23–5



THE NUTRITIONAL STATE REGULATES LIPOGENESIS

Excess carbohydrate is stored as fat in many animals in anticipation of periods of caloric deficiency such as starvation, hibernation, etc, and to provide energy for use between meals in animals, including humans, that take their food at spaced intervals. Lipogenesis converts surplus glucose and intermediates such as pyruvate, lactate, and acetyl-CoA to fat, assisting the anabolic phase of this feeding cycle. The nutritional state of the organism is the main factor regulating the rate of lipogenesis. Thus, the rate is high in the well-fed animal whose diet contains a high proportion of carbohydrate. It is depressed by restricted caloric intake, high-fat diet, or a deficiency of insulin, as in diabetes mellitus. These latter conditions are associated with increased concentrations of plasma-free fatty acids, and an inverse relationship has been demonstrated between hepatic lipogenesis and the concentration of serum free fatty acids. Lipogenesis is increased when sucrose is fed instead of glucose because fructose bypasses the phosphofructokinase control point in glycolysis and floods the lipogenic pathway .



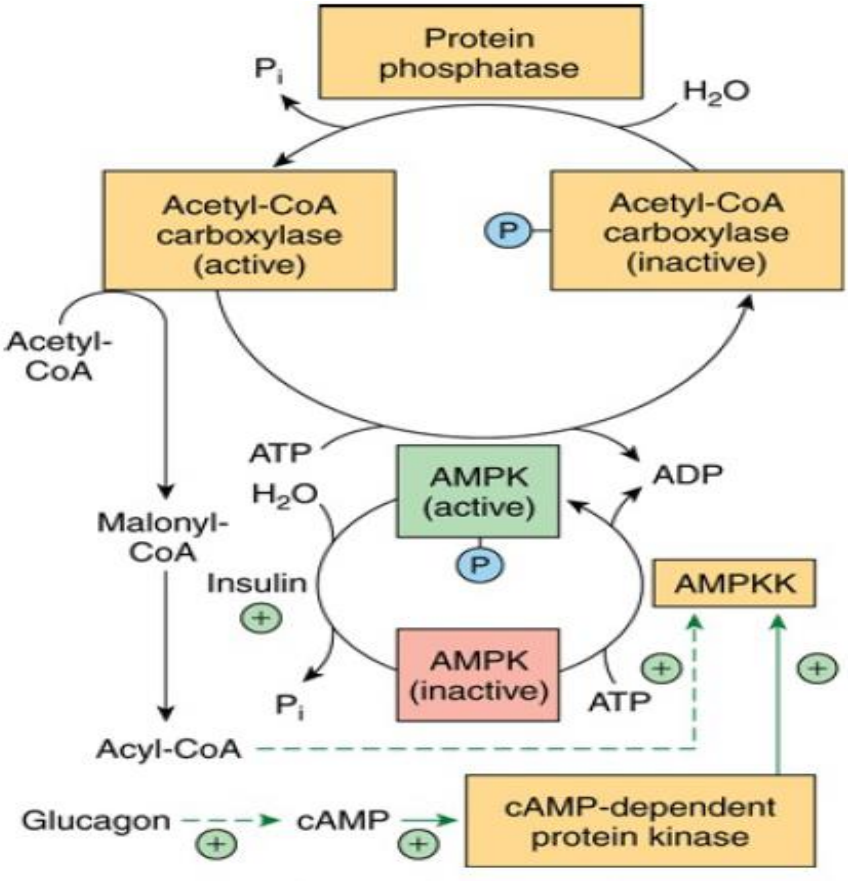
SHORT- & LONG-TERM MECHANISMS REGULATE LIPOGENESIS

Long-chain fatty acid synthesis is controlled in the short term by allosteric and covalent modification of enzymes and in the long term by changes in gene expression governing rates of synthesis of enzymes.

Acetyl-CoA Carboxylase Is the Most Important Enzyme in the Regulation of Lipogenesis

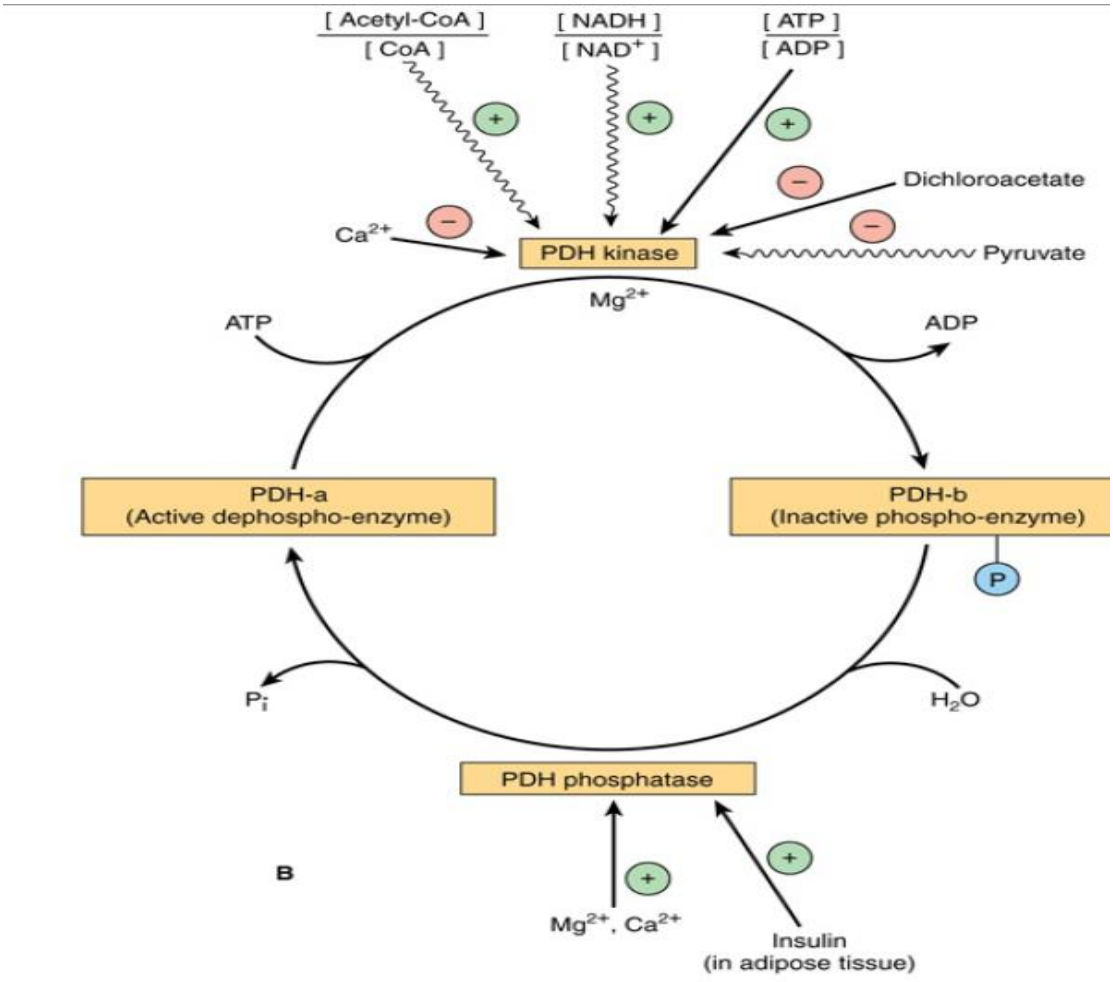
Acetyl-CoA carboxylase is an allosteric enzyme and is activated by **citrate,** which increases in concentration in the well-fed state and is an indicator of a plentiful supply of acetyl-CoA.

Citrate promotes the conversion of the enzyme from an inactive dimer to an active polymeric form, with a molecular mass of several million. Inactivation is promoted by phosphorylation of the enzyme and by long-chain acyl-CoA molecules, an example of negative feedback inhibition by a product of a reaction . Thus, if acyl-CoA accumulates because it is not esterified quickly enough or because of increased lipolysis or an influx of free fatty acids into the tissue, it will automatically reduce the synthesis of new fatty acid. Acyl-CoA also inhibits the mitochondrial **tricarboxylate transporter,** thus preventing activation of the enzyme by egress of citrate from the mitochondria into the cytosol. Acetyl-CoA carboxylase is also regulated by hormones such as **glucagon, epinephrine,** and **insulin** via changes in its phosphorylation state.



Pyruvate Dehydrogenase Is Also Regulated by Acyl-CoA

Acyl-CoA causes an inhibition of pyruvate dehydrogenase by inhibiting the ATP–ADP exchange transporter of the inner mitochondrial membrane, which leads to increased intramitochondrial (ATP)/(ADP) ratios and therefore to conversion of active to inactive pyruvate dehydrogenase (see Figure 18–6), thus regulating the availability of acetyl-CoA for lipogenesis. Furthermore, oxidation of acyl-CoA due to increased levels of free fatty acids may increase the ratios of (acetyl CoA)/(CoA) and (NADH)/(NAD+) in mitochondria, inhibiting pyruvate dehydrogenase.



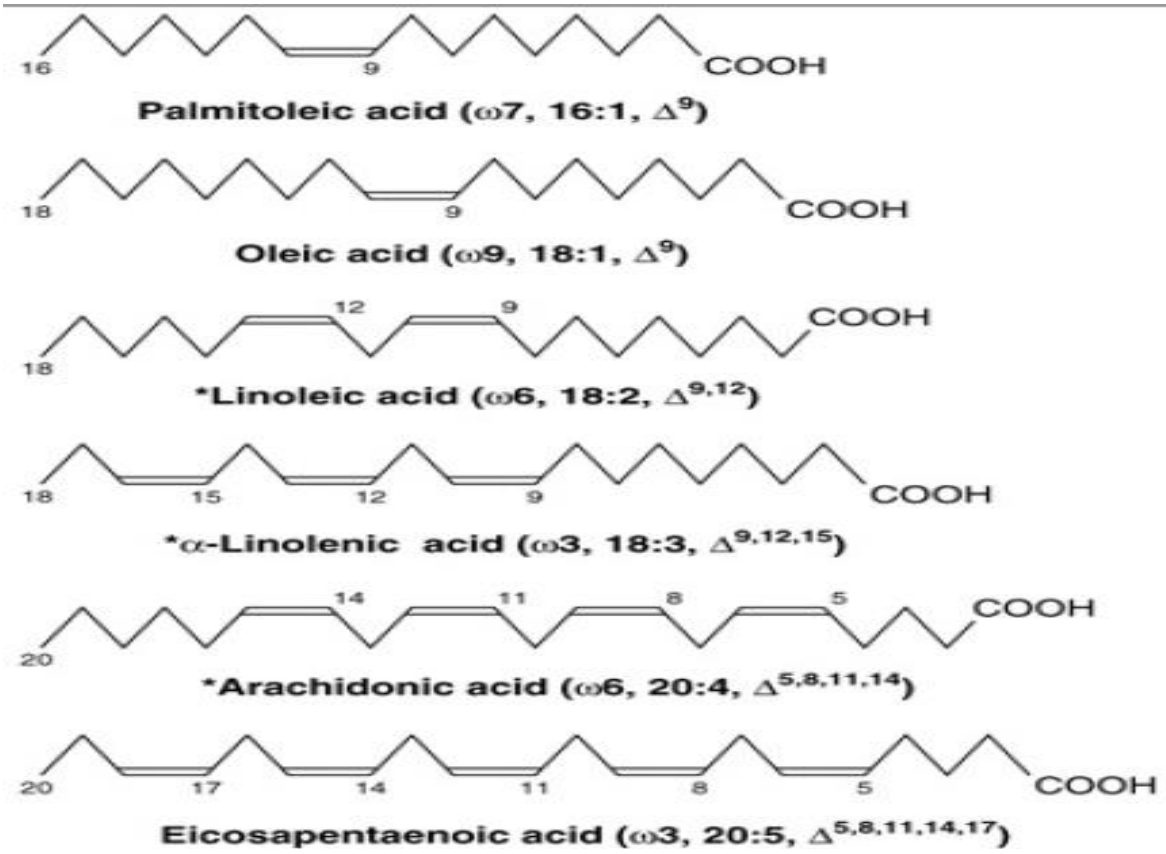
Insulin Also Regulates Lipogenesis by Other Mechanisms

Insulin stimulates lipogenesis by several other mechanisms as well as by increasing acetyl-CoA carboxylase activity. It increases the transport of glucose into the cell (eg, in adipose tissue), increasing the availability of both pyruvate for fatty acid synthesis and glycerol 3-phosphate for esterification of the newly

formed fatty acids, and also converts the inactive form of pyruvate dehydrogenase to the active form in adipose tissue, but not in liver. Insulin also—by its ability to depress the level of intracellular cAMP—**inhibits lipolysis** in adipose tissue and reducing the concentration of plasma-free fatty acids and, therefore, long-chain acyl-CoA, which are inhibitors of lipogenesis.

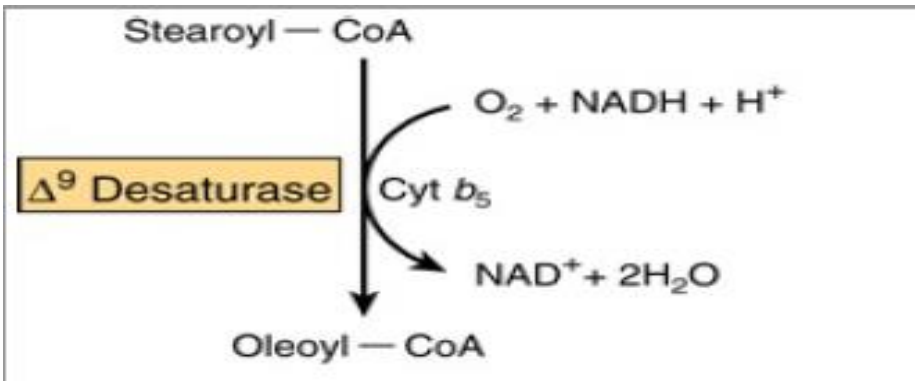
SOME POLYUNSATURATED FATTY ACIDS CANNOT BE SYNTHESIZED BY MAMMALS & ARE NUTRITIONALLY ESSENTIAL

Certain long-chain unsaturated fatty acids of metabolic significance in mammals are shown in Figure 23–8. Other C20, C22, and C24 polyenoic fatty acids may be derived from oleic, linoleic, and -linolenic acids by chain elongation. Palmitoleic and oleic acids are not essential in the diet because the tissues can introduce a double bond at the Δ9 position of a saturated fatty acid. **Linoleic and α-linolenic acids** are the only fatty acids known to be essential for the complete nutrition of many species of animals, including humans, and are termed the **nutritionally essential fatty acids.** In most mammals, **arachidonic acid** can be formed from linoleic acid (Figure 23–11). Double bonds can be introduced at the Δ4, Δ5, Δ6, and Δ9 positions in most animals, but never beyond the Δ9 position. In contrast, plants are able to synthesize the nutritionally essential fatty acids by introducing double bonds at the Δ12 and Δ15 positions.



MONOUNSATURATED FATTY ACIDS ARE SYNTHESIZED BY A 9 DESATURASE SYSTEM

Several tissues including the liver are considered to be responsible for the formation of nonessential monounsaturated fatty acids from saturated fatty acids. The first double bond introduced into a saturated fatty acid is nearly always in the Δ9 position. An enzyme system—Δ9**desaturase** in the endoplasmic reticulum catalyzes the conversion of palmitoyl-CoA or stearoyl-CoA to palmitoleoyl-CoA or oleoyl-CoA, respectively. Oxygen and either NADH or NADPH are necessary for the reaction. The enzymes appear to be similar to a mono-oxygenase system involving cytochrome *b*5.

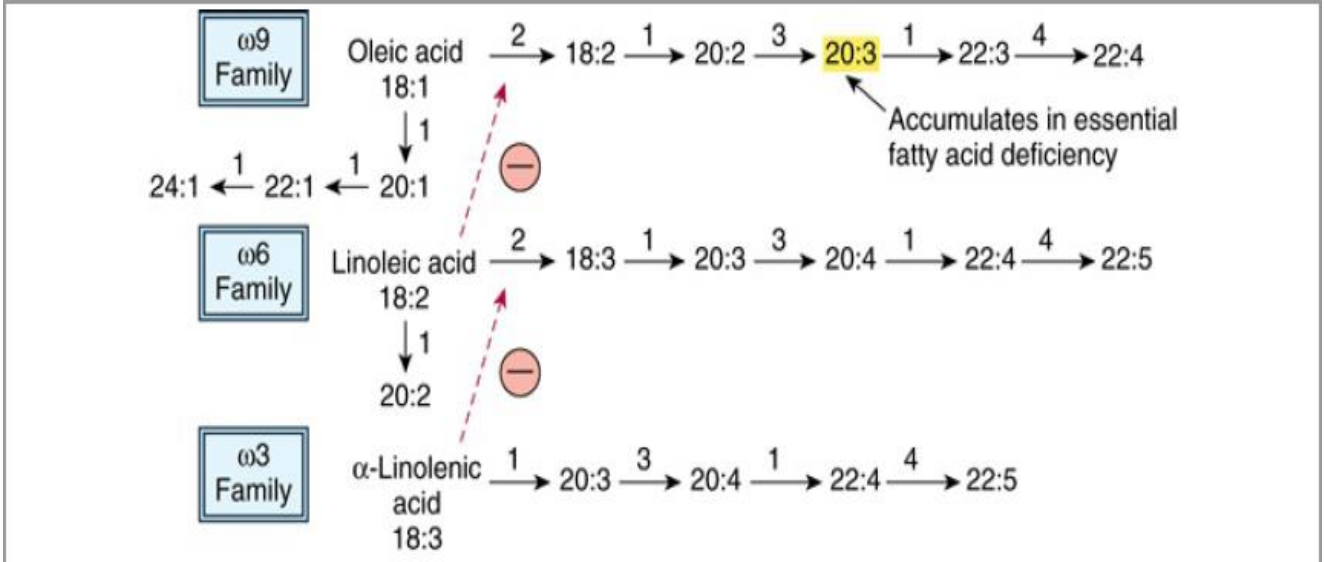


SYNTHESIS OF POLYUNSATURATED FATTY ACIDS INVOLVES DESATURASE & ELONGASE ENZYME SYSTEMS

Additional double bonds introduced into existing monounsaturated fatty acids are always separated from each other by a methylene group (methylene interrupted) except in bacteria.

Since animals have a Δ9 desaturase, they are able to synthesize the Δ9 (oleic acid) family of unsaturated fatty acids completely by a combination of chain elongation and desaturation (Figure 23–10). However, as indicated above, linoleic (ω6) or α-linolenic (ω3) acids required for the synthesis of the other members of the ω6 or ω3 families must be supplied in the diet. Linoleate may be converted to arachidonate via **α-linolenate** by the pathway shown in Figure 23–11. The nutritional requirement for arachidonate may thus be dispensed with if there is adequate linoleate in the diet. The desaturation and chain elongation system is greatly diminished in the starving state, in response to glucagon and epinephrine administration, and in the absence of insulin as in type 1 diabetes mellitus.

Figure 23–10



1: elongase, 2: Δ6 desaturase, 3:Δ 5 desaturase, 4: Δ4 desaturase

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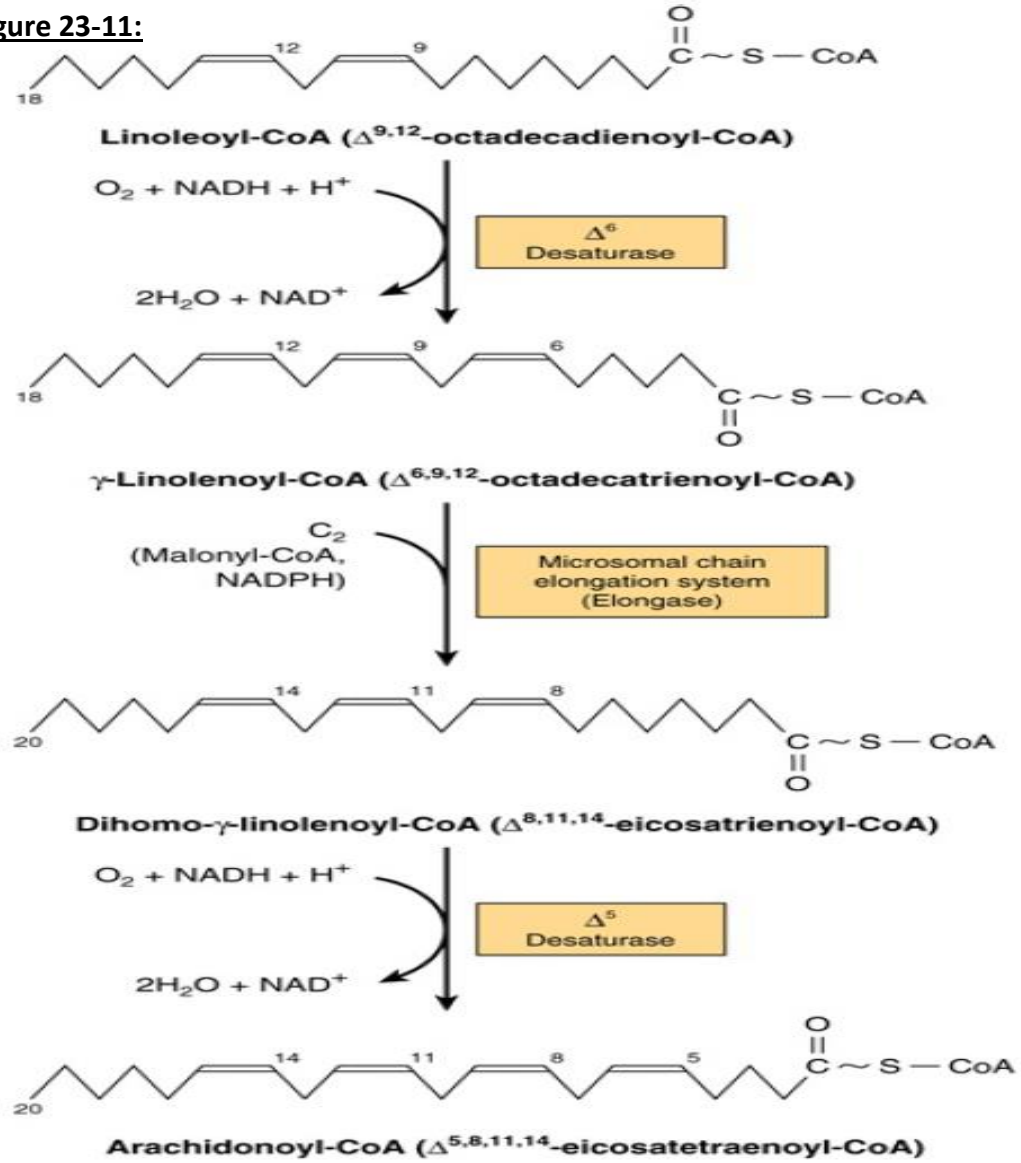
Figure 23-11:



OXIDATION OF FATTY ACIDS: KETOGENESIS

BIOMEDICAL IMPORTANCE

Although fatty acids are broken down by oxidation to acetyl-CoA and also synthesized from acetyl-CoA, fatty acid oxidation is not the simple reverse of fatty acid biosynthesis but an entirely different process taking place in a separate compartment of the cell. The separation of fatty acid oxidation in mitochondria from biosynthesis in the cytosol allows each process to be individually controlled and integrated with tissue requirements. Each step in fatty acid oxidation involves acyl-CoA derivatives, is catalyzed by separate enzymes, utilizes NAD+ and FAD as coenzymes, and generates ATP. It is an aerobic process, requiring the presence of oxygen.

Increased fatty acid oxidation is a characteristic of starvation and of diabetes mellitus, and leads to **ketone body** production by the liver **(ketosis).** Ketone bodies are acidic and when produced in excess over long periods, as in diabetes, cause **ketoacidosis,** which is ultimately fatal. Because gluconeogenesis is dependent upon fatty acid oxidation, any impairment in fatty acid oxidation leads to **hypoglycemia.** This occurs in various states of **carnitine deficiency** or deficiency of essential enzymes in fatty acid oxidation, for example, **carnitine palmitoyltransferase,** or inhibition of fatty acid oxidation by poisons, for example, **hypoglycin.**

OXIDATION OF FATTY ACIDS OCCURS IN MITOCHONDRIA

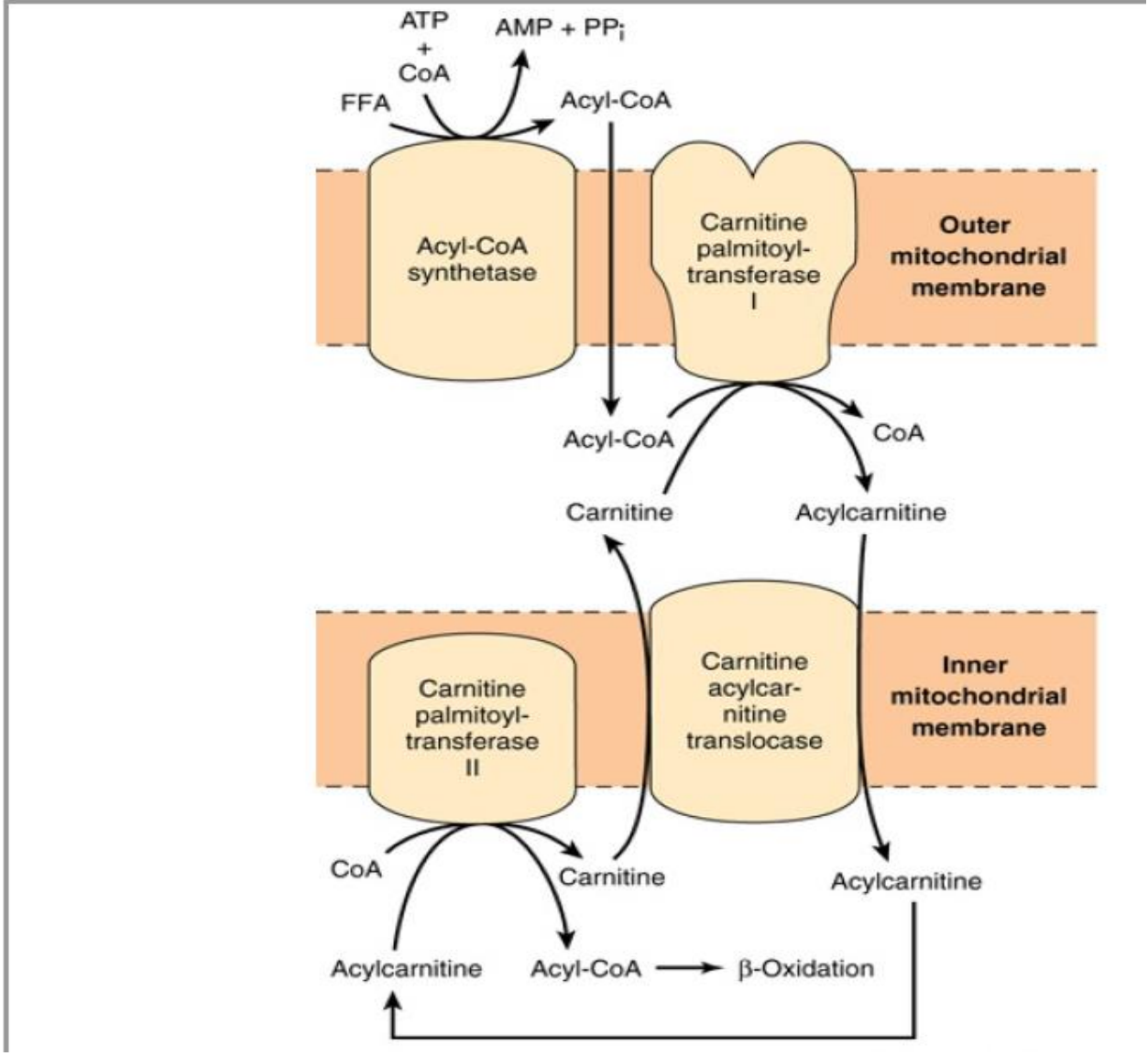
Fatty Acids Are Transported in the Blood as Free Fatty Acids

Free fatty acids (FFA)—also called unesterified (UFA) or nonesterified (NEFA) fatty acids—are fatty acids that are in the **unesterified state.** In plasma, longer chain FFA are combined with **albumin,** and in the cell they are attached to a **fatty acid binding protein,** so that in fact they are never really "free." Shorter chain fatty acids are more water-soluble and exist as the unionized acid or as a fatty acid anion.

Fatty Acids Are Activated before Being Catabolized

Fatty acids must first be converted to an active intermediate before they can be catabolized. This is the only step in the complete degradation of a fatty acid that requires energy from ATP. In the presence of ATP and coenzyme A, the enzyme **acyl-CoA synthetase (thiokinase)** catalyzes the conversion of a fatty acid (or FFA) to an "active fatty acid" or acyl-CoA, which uses one high-energy phosphate with the formation of AMP and PP*i* (Figure 22–1). The PP*i* is hydrolyzed by **inorganic pyrophosphatase** with the loss of a further high-energy phosphate, ensuring that the overall reaction goes to completion. Acyl-CoA synthetases are found in the endoplasmic reticulum, peroxisomes, and inside and on the outer membrane of mitochondria.

Figure 22–1



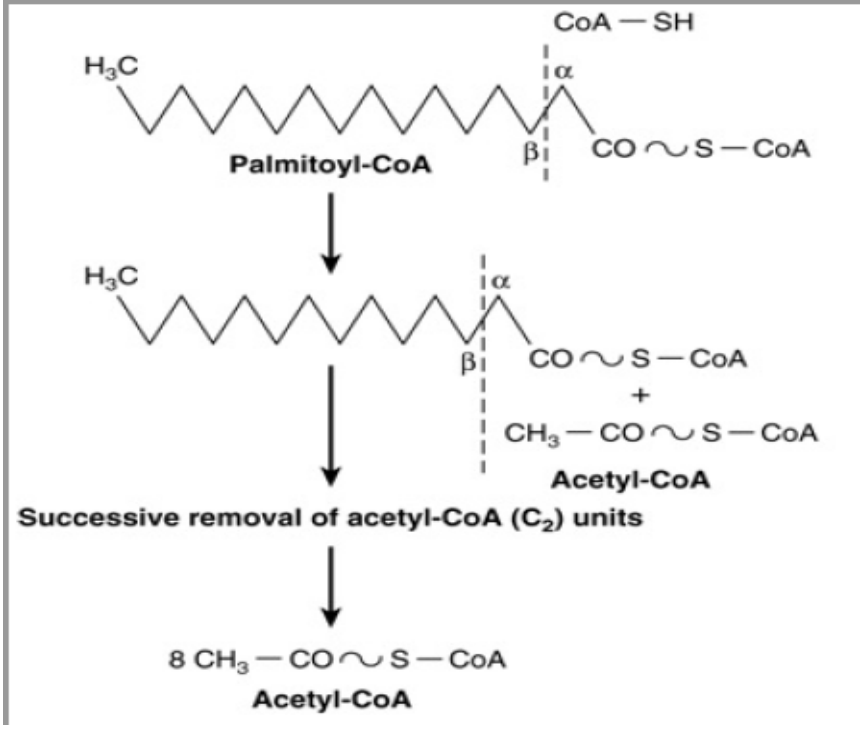
Long-Chain Fatty Acids Penetrate the Inner Mitochondrial Membrane as Carnitine Derivatives

Carnitine (β-hydroxy-γ-trimethylammonium butyrate), $(CH_3)_3N^+—CH_2—CH(OH)—CH_2—COO^-$, is widely distributed and is particularly abundant in muscle. Long-chain acyl-CoA (or FFA) cannot penetrate the inner membrane of mitochondria. In the presence of carnitine, however, **carnitine palmitoyltransferase-I,** located in the outer mitochondrial membrane, converts long-chain acyl-CoA to **acylcarnitine,** which is able to penetrate the inner membrane and gain access to the β-oxidation system of enzymes (Figure 22–1). **Carnitineacylcarnitine translocase** acts as an inner membrane exchange transporter. Acylcarnitine is transported in, coupled with the transport out of one molecule of carnitine. The acylcarnitine then reacts with CoA, catalyzed by **carnitine palmitoyltransferase-II,** located on the inside of the inner membrane, reforming acyl-CoA in the mitochondrial matrix, and carnitine is liberated.

β-OXIDATION OF FATTY ACIDS INVOLVES SUCCESSIVE CLEAVAGE WITH RELEASE OF ACETYL-COA

In **β-oxidation** (Figure 22–2), two carbons at a time are cleaved from acyl-CoA molecules, starting at the carboxyl end. The chain is broken between the α(2)- and β(3)-carbon atoms—hence the name β-oxidation. The two-carbon units formed are acetyl-CoA; thus, palmitoyl-CoA forms eight acetyl-CoA molecules.

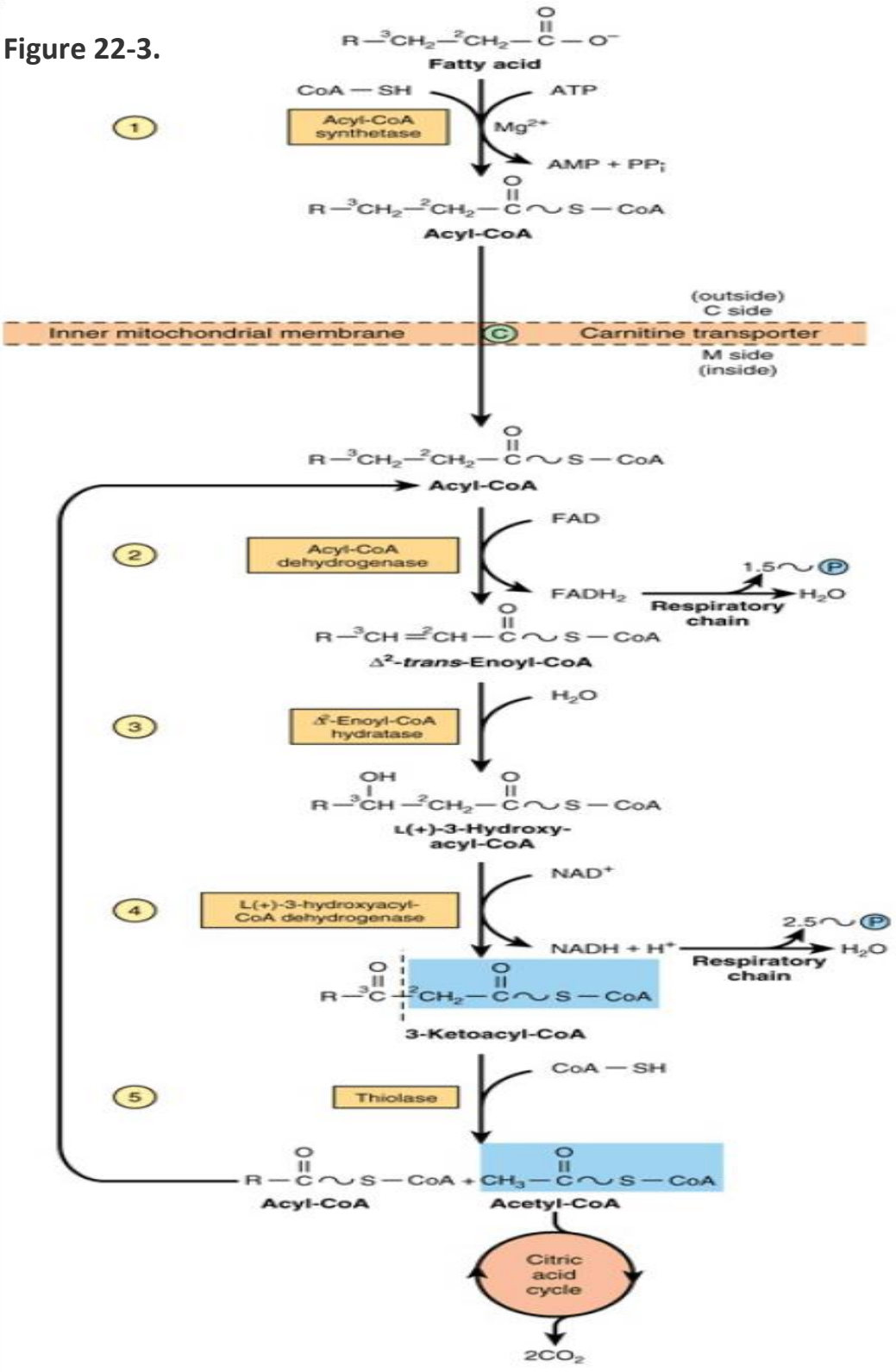
Figure 22–2



The Cyclic Reaction Sequence Generates FADH2 & NADH

Several enzymes, known collectively as "fatty acid oxidase," are found in the mitochondrial matrix or inner membrane adjacent to the respiratory chain. These catalyze the oxidation of acyl-CoA to acetyl-CoA, the system being coupled with the phosphorylation of ADP to ATP (Figure 22–3).

Figure 22-3.



The first step is the removal of two hydrogen atoms from the 2(α)- and 3(β)-carbon atoms, catalyzed by **acyl-CoA dehydrogenase** and requiring FAD. This results in the formation of Δ2-*trans*-enoyl-CoA and FADH2. The reoxidation of FADH2 by the respiratory chain requires the mediation of another flavoprotein, termed **electron-transferring flavoprotein**. Water is added to saturate the double bond and form 3-hydroxyacyl-CoA, catalyzed by **Δ2-enoyl-CoA hydratase.** The 3-hydroxy derivative undergoes further dehydrogenation on the 3-carbon catalyzed by **L(+)-3-hydroxyacyl-CoA dehydrogenase** to form the corresponding 3-ketoacyl-CoA compound. In this case, NAD+ is the coenzyme involved. Finally, 3-ketoacyl-CoA is split at the 2,3-position by **thiolase** (3-ketoacyl-CoA-thiolase), forming acetyl-CoA and a new acyl-CoA two carbons shorter than the original acyl-CoA molecule. The acyl-CoA formed in the cleavage reaction reenters the oxidative pathway at reaction 2 (Figure 22–3). In this way, a long-chain fatty acid may be degraded completely to acetyl-CoA (C2 units). Since acetyl-CoA can be oxidized to CO2 and water via the citric acid cycle (which is also found within the mitochondria), the complete oxidation of fatty acids is achieved.

Oxidation of a Fatty Acid with an Odd Number of Carbon Atoms Yields Acetyl-CoA Plus a Molecule of Propionyl-CoA

Fatty acids with an odd number of carbon atoms are oxidized by the pathway of β-oxidation, producing acetyl-CoA, until a three-carbon (propionyl-CoA) residue remains. This compound is converted to succinyl-CoA, a constituent of the citric acid cycle . Hence, **the propionyl residue from an odd-chain fatty acid is the only part of a fatty acid that is glucogenic.**

Oxidation of Fatty Acids Produces a Large Quantity of ATP

Transport of electrons from FADH2 and NADH via the respiratory chain leads to the synthesis of four high-energy phosphates for each of the seven cycles needed for the breakdown of the C16 fatty acid, palmitate, to acetyl-CoA (7 x 4 = 28). A total of 8 mol of acetyl-CoA is formed, and each gives rise to 10 mol of ATP on oxidation in the citric acid cycle, making 8 x 10 = 80 mol. Two must be subtracted for the initial activation of the fatty acid, yielding a net gain of 106 mol of ATP per mole of palmitate, or 106 x 51.6*= 5470 kJ. This represents 68% of the free energy of combustion of palmitic acid.

Peroxisomes Oxidize Very Long Chain Fatty Acids

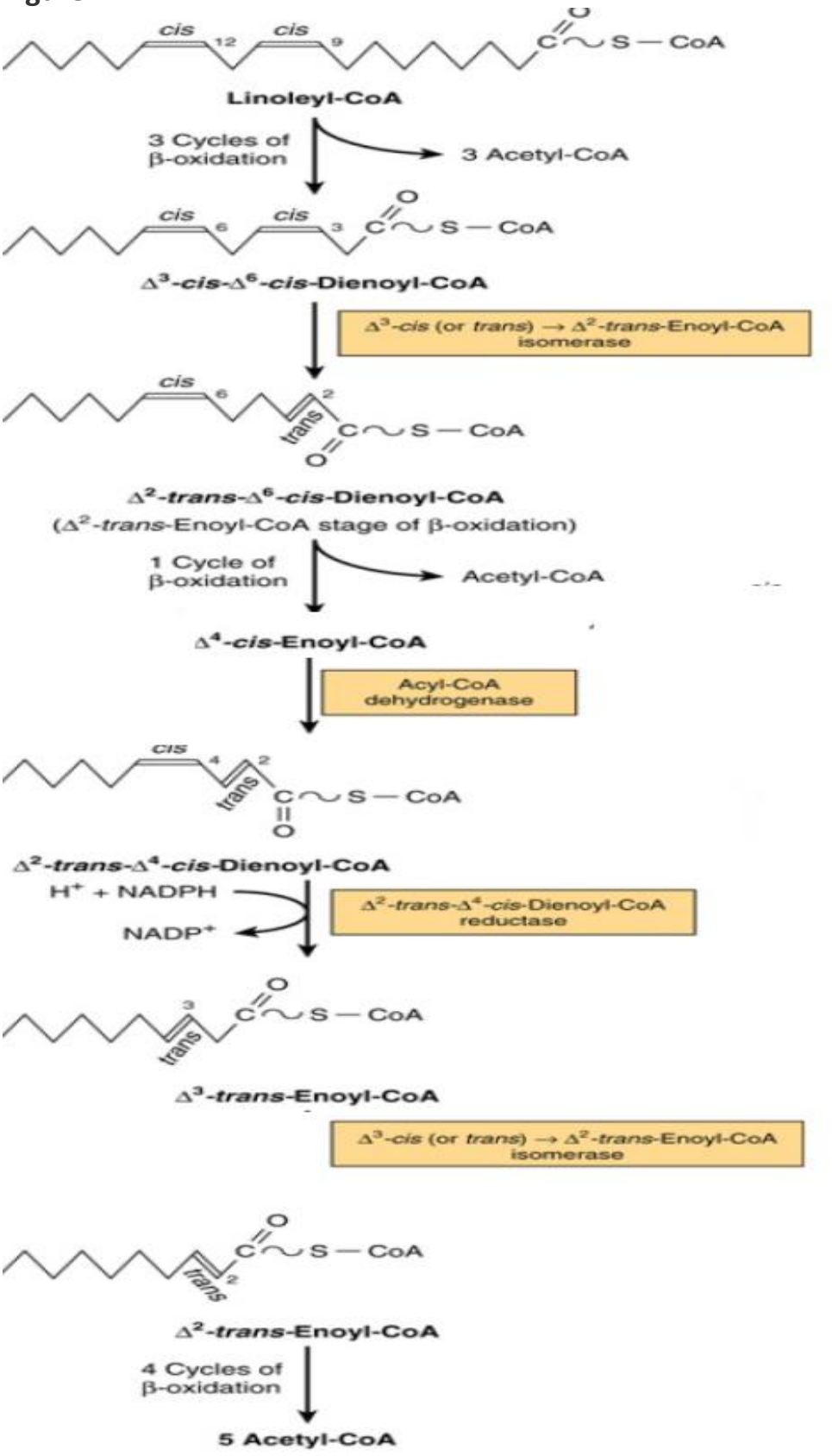
A modified form of β-oxidation is found in **peroxisomes** and leads to the formation of acetyl-CoA and H2O2 (from the flavoprotein-linked dehydrogenase step), which is broken down by catalase . Thus, this dehydrogenation in peroxisomes is not linked directly to phosphorylation and the generation of ATP. The system facilitates the oxidation of **very long chain fatty acids** (eg, C20, C22). These enzymes are induced by high-fat diets and in some species by hypolipidemic drugs such as clofibrate.

The enzymes in peroxisomes do not attack shorter chain fatty acids; the β-oxidation sequence ends at octanoyl-CoA. Octanoyl and acetyl groups are both further oxidized in mitochondria. Another role of peroxisomal β-oxidation is to shorten the side chain of cholesterol in bile acid formation . Peroxisomes also take part in the synthesis of ether glycerolipids, cholesterol, and dolichol .

OXIDATION OF UNSATURATED FATTY ACIDS OCCURS BY A MODIFIED β-OXIDATION PATHWAY

The CoA esters of unsaturated fatty acids are degraded by the enzymes normally responsible for β-oxidation until either a Δ3-*cis*-acyl-CoA compound or a Δ4-*cis*-acyl-CoA compound is formed, depending upon the position of the double bonds (Figure 22–4). The former compound is isomerized **(Δ3cis or trans ⟶ Δ2-*trans*-*enoyl-CoA isomerase)*** to the corresponding Δ2-*trans*-CoA stage of β-oxidation for subsequent hydration and oxidation. Any Δ4-*cis*-acyl-CoA either remaining, as in the case of linoleic acid, or entering the pathway at this point after conversion by acyl-CoA dehydrogenase to Δ2-*trans*- *Δ*4-*cis*-dienoyl-CoA, is then metabolized as indicated in Figure 22–4.

Figure 22–4.

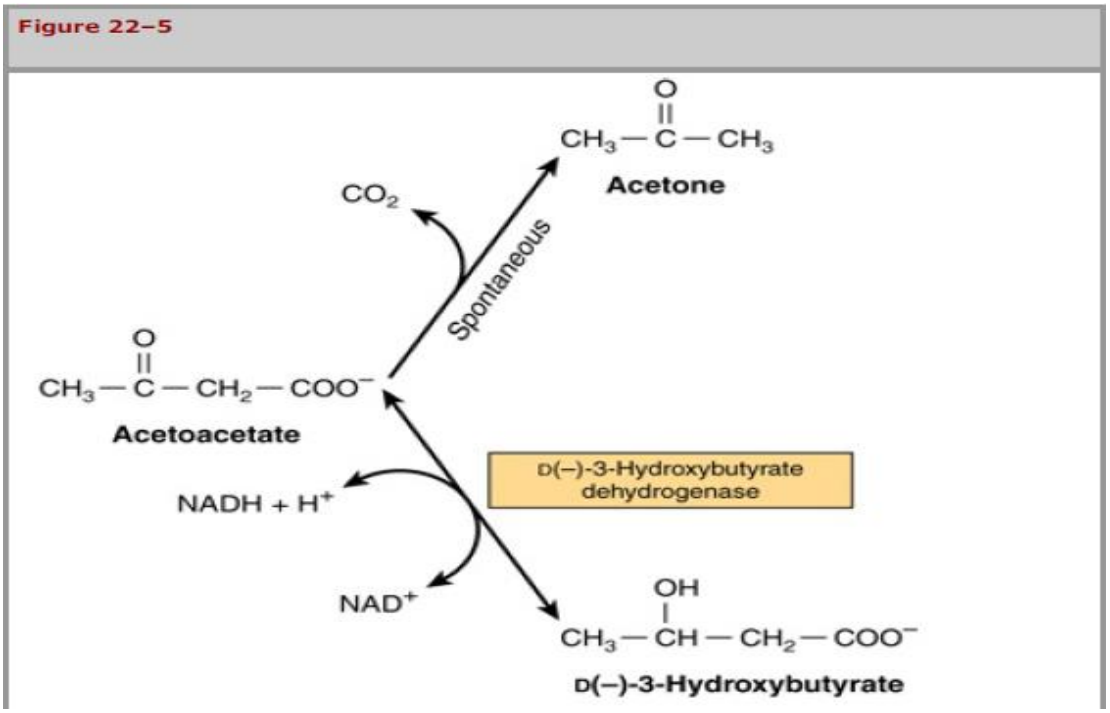

cis
12
cis
9
S — CoA
Linoleyl-CoA
3 Cycles of β-oxidation
3 Acetyl-CoA
cis
6
cis
3
S — CoA
Δ3-cis-Δ6-cis-Dienoyl-CoA
Δ3-cis (or trans) → Δ2-trans-Enoyl-CoA isomerase
cis
6
trans
2
S — CoA
Δ2-trans-Δ6-cis-Dienoyl-CoA
(Δ2-trans-Enoyl-CoA stage of β-oxidation)
1 Cycle of β-oxidation
Acetyl-CoA
Δ4-cis-Enoyl-CoA
Acyl-CoA dehydrogenase
cis
4
trans
2
S — CoA
Δ2-trans-Δ4-cis-Dienoyl-CoA
H+ + NADPH
NADP+
Δ2-trans-Δ4-cis-Dienoyl-CoA reductase
trans
3
S — CoA
Δ3-trans-Enoyl-CoA
Δ3-cis (or trans) → Δ2-trans-Enoyl-CoA isomerase
trans
2
S — CoA
Δ2-trans-Enoyl-CoA
4 Cycles of β-oxidation
5 Acetyl-CoA

OXIDATION OF FATTY ACIDS: KETOGENESIS

KETOGENESIS OCCURS WHEN THERE IS A HIGH RATE OF FATTY-ACID OXIDATION IN THE LIVER

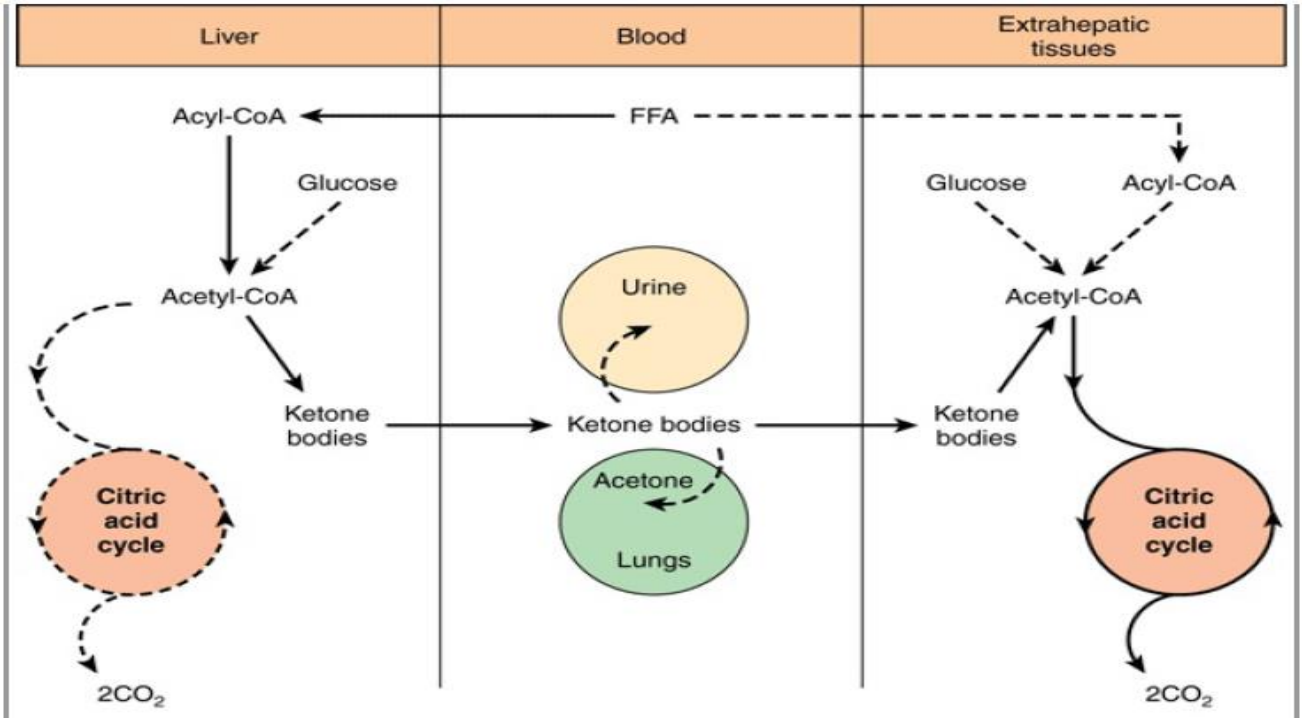
Under metabolic conditions associated with a high rate of fatty acid oxidation, the liver produces considerable quantities of **acetoacetate** and **D(–)-3 hydroxybutyrate** (β-hydroxybutyrate). Acetoacetate continually undergoes spontaneous decarboxylation to yield **acetone.** These three substances are collectively known as the **ketone bodies** (also called acetone bodies or [incorrectly*] "ketones") (Figure 22–5). Acetoacetate and 3-hydroxybutyrate are interconverted by the mitochondrial enzyme D**(–)-3-hydroxybutyrate dehydrogenase;** the equilibrium is controlled by the mitochondrial [NAD+]/[NADH] ratio, ie, the **redox state.** The concentration of total ketone bodies in the blood of well-fed mammals does not normally exceed 0.2 mmol/L except in ruminants, where 3-hydroxybutyrate is formed continuously from butyric acid (a product of ruminal fermentation) in the rumen wall. In vivo, the liver appears to be the only organ in nonruminants to add significant quantities of ketone bodies to the blood. Extrahepatic tissues utilize them as respiratory substrates. The net flow of ketone bodies from the liver to the extrahepatic tissues results from active hepatic synthesis coupled with very low utilization. The reverse situation occurs in extrahepatic tissues (Figure 22–6).

Figure 22–5



*The term "ketones" should not be used because 3-hydroxybutyrate is not a ketone and there are ketones in blood that are not ketone bodies, for example, pyruvate and fructose.

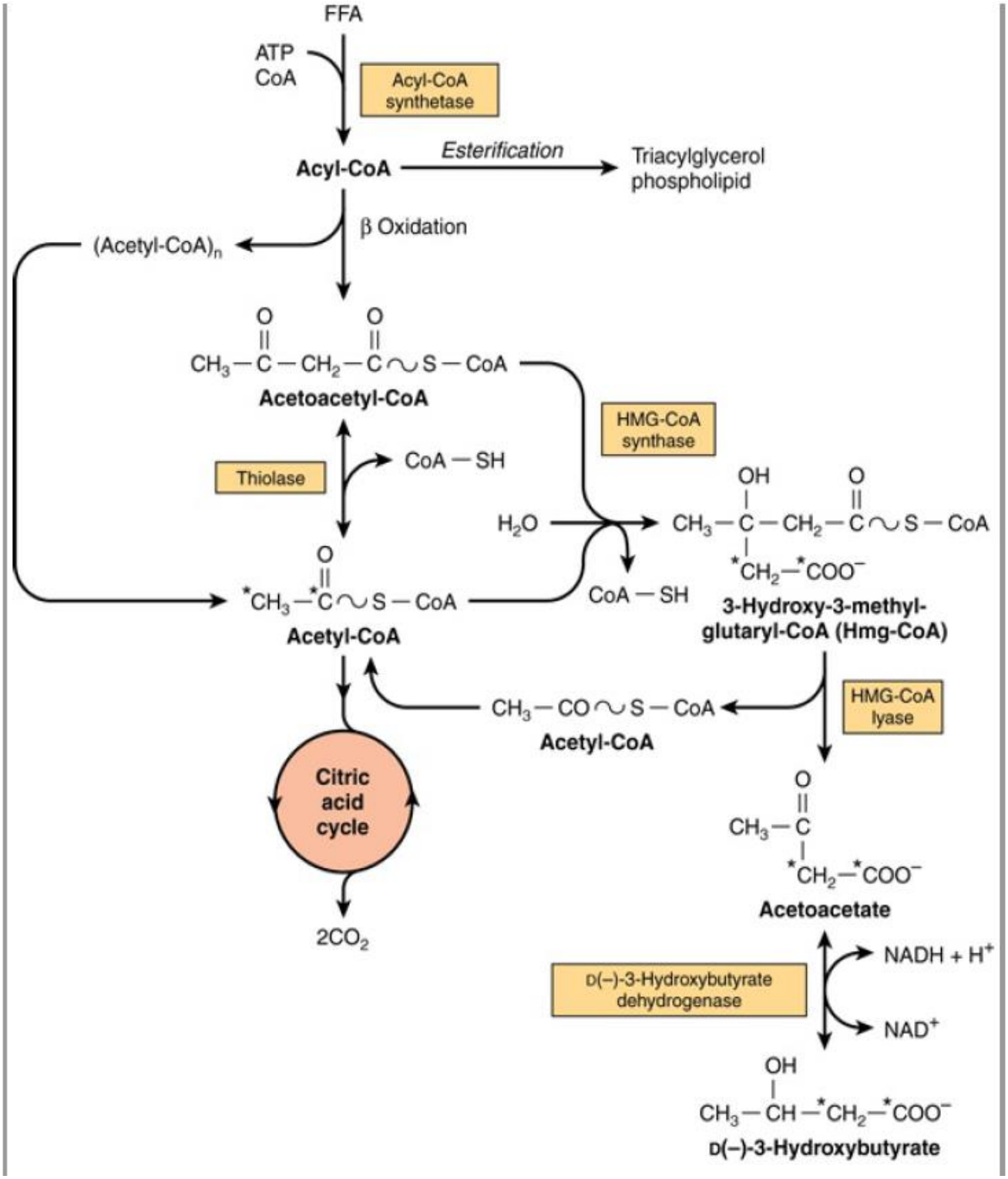
Figure 22–6.



3-Hydroxy-3-Methylglutaryl-CoA (HMG-CoA) Is an Intermediate in the Pathway of Ketogenesis

Enzymes responsible for ketone body formation are associated mainly with the mitochondria. Two acetyl-CoA molecules formed in β-oxidation condense to form acetoacetyl-CoA by a reversal of the **thiolase** reaction. Acetoacetyl-CoA, which is the starting material for ketogenesis, also arises directly from the terminal four carbons of a fatty acid during β–oxidation (Figure 22–7). Condensation of acetoacetyl-CoA with another molecule of acetyl-CoA by **3-hydroxy-3-methylglutaryl-CoA synthase** forms 3-hydroxy-3-methylglutaryl-CoA **(HMGCoA).**
3-Hydroxy-3-methylglutaryl-CoA lyase then causes acetyl-CoA to split off from the HMG-CoA, leaving free acetoacetate. The carbon atoms split off in the acetyl-CoA molecule are derived from the original acetoacetyl-CoA molecule. **Both**

enzymes must be present in mitochondria for ketogenesis to take place. This occurs solely in liver and rumen epithelium. D(–)-3-Hydroxybutyrate is quantitatively the predominant ketone body present in the blood and urine in ketosis.

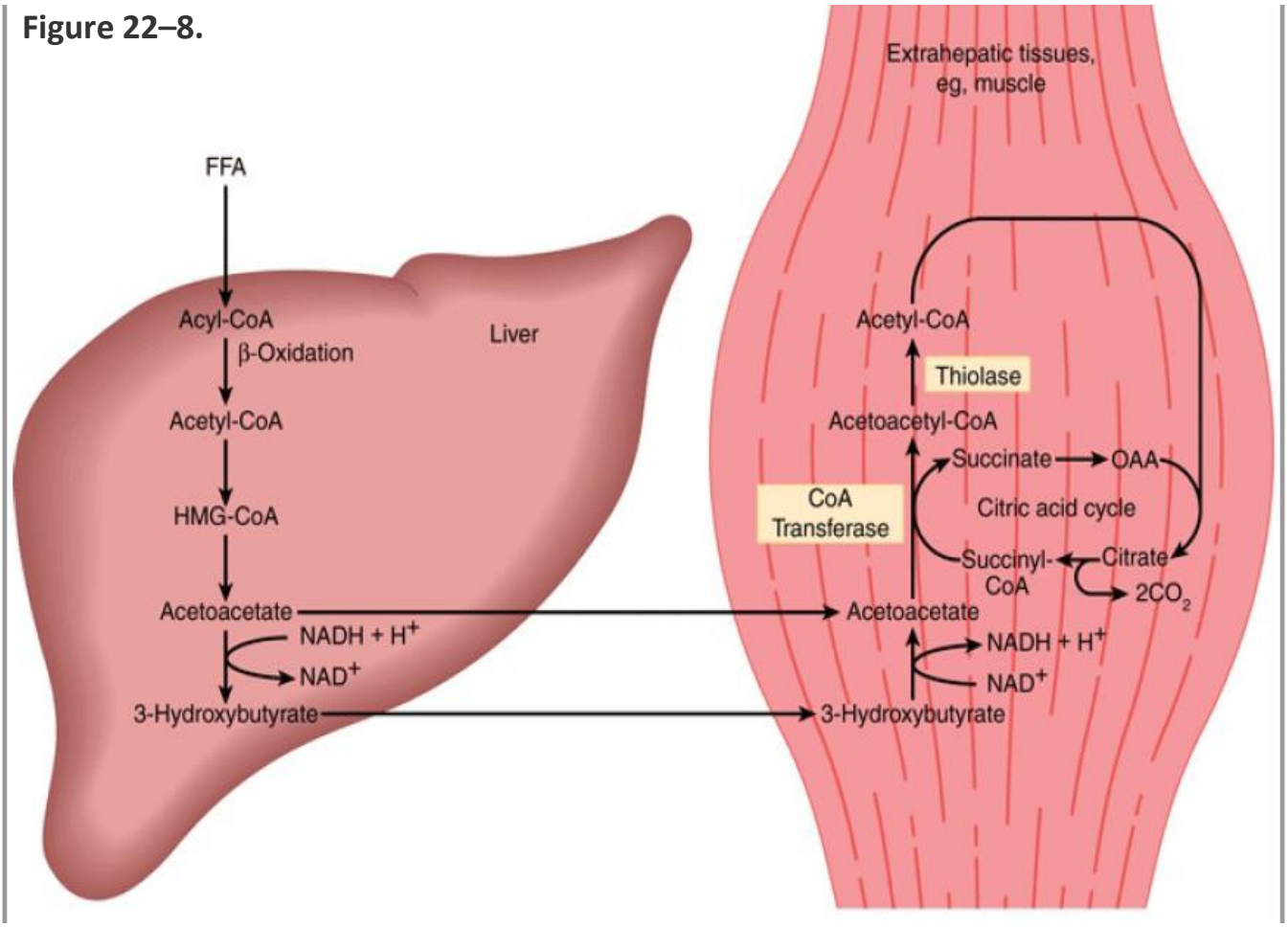


Ketone Bodies Serve as a Fuel for Extrahepatic Tissues

While an active enzymatic mechanism produces acetoacetate from acetoacetyl-CoA in the liver, acetoacetate once formed cannot be reactivated directly except in the cytosol, where it is used in a much less active pathway as a precursor in cholesterol synthesis. This accounts for the net production of ketone bodies by the liver.

In extrahepatic tissues, acetoacetate is activated to acetoacetyl-CoA by **succinyl-CoA-acetoacetate CoA transferase.** CoA is transferred from succinyl-CoA to form acetoacetyl-CoA (Figure 22–8). With the addition of a CoA, the acetoacetyl-CoA is split into two acetyl-CoAs by thiolase and oxidized in the citric acid cycle. If the blood level is raised, oxidation of ketone bodies increases until, at a concentration of ~12 mmol/L, the oxidative machinery is saturated. When this occurs, a large proportion of oxygen consumption may be accounted for by the oxidation of ketone bodies.

Figure 22–8.



In most cases, **ketonemia is due to increased production of ketone bodies** by the liver rather than to a deficiency in their utilization by extrahepatic tissues. While acetoacetate and D(–)-3-hydroxybutyrate are readily oxidized by extrahepatic tissues, acetone is difficult to oxidize in vivo and to a large extent is volatilized in the lungs.

In moderate ketonemia, the loss of ketone bodies via the urine is only a few percent of the total ketone body production and utilization. Since there are renal threshold-like effects (there is not a true threshold) that vary between species and individuals, measurement of the ketonemia, not the ketonuria, is the preferred method of assessing the severity of ketosis.

KETOGENESIS IS REGULATED AT THREE CRUCIAL STEPS

1. Ketosis does not occur in vivo unless there is an increase in the level of circulating FFA that arise from lipolysis of triacylglycerol in adipose tissue. **FFA are the precursors of ketone bodies in the liver.** The liver, both in fed and in fasting conditions, extracts ~30% of the FFA passing through it, so that at high concentrations the flux passing into the liver is substantial. **Therefore, the factors regulating mobilization of FFA from adipose tissue are important in controlling ketogenesis** (Figures 22–9 and 25–8).

2. After uptake by the liver, FFA are either **β-oxidized** to CO2 or ketone bodies or **esterified** to triacylglycerol and phospholipid. There is regulation of entry of fatty acids into the oxidative pathway by **carnitine palmitoyltransferase-I** (CPT-I), and the remainder of the fatty acid taken up is esterified. CPT-I activity is low in the fed state, leading to depression of fatty acid oxidation, and high in starvation, allowing fatty acid oxidation to increase. **Malonyl-CoA,** the initial intermediate in fatty acid biosynthesis (Figure 23–1) formed by acetyl-CoA carboxylase in the fed state, is a potent inhibitor of CPT-I (Figure 22–10). Under these conditions, FFA enter the liver cell in low concentrations and are nearly all esterified to acylglycerols and transported out of the liver in **very low density lipoproteins** (VLDL). However, as the concentration of FFA increases with the onset of starvation, acetyl-CoA carboxylase is inhibited directly by acyl-CoA, and (malonyl-CoA) decreases, releasing the inhibition of CPT-I and allowing more acyl-CoA to be β-oxidized. These events are reinforced in starvation by a decrease in the **(insulin)/(glucagon) ratio.** Thus, β-oxidation from FFA is controlled by the CPT-I

gateway into the mitochondria, and the balance of the FFA uptake not oxidized is esterified.

3. In turn, the acetyl-CoA formed in β-oxidation is oxidized in the citric acid cycle, or it enters the pathway of ketogenesis to form ketone bodies. As the level of serum FFA is raised, proportionately more FFA is converted to ketone bodies and less is oxidized via the citric acid cycle to CO2. The partition of acetyl-CoA between the ketogenic pathway and the pathway of oxidation to CO2 is regulated so that the total free energy captured in ATP which results from the oxidation of FFA remains constant as their concentration in the serum changes. This may be appreciated when it is realized that complete oxidation of 1 mol of palmitate involves a net production of 106 mol of ATP via β–oxidation and CO2 production in the citric acid cycle (see above), whereas only 26 mol of ATP are produced when acetoacetate is the end product and only 21 mol when 3- hydroxybutyrate is the end product. Thus, ketogenesis may be regarded as a mechanism that allows the liver to oxidize increasing quantities of fatty acids within the constraints of a tightly coupled system of oxidative phosphorylation.

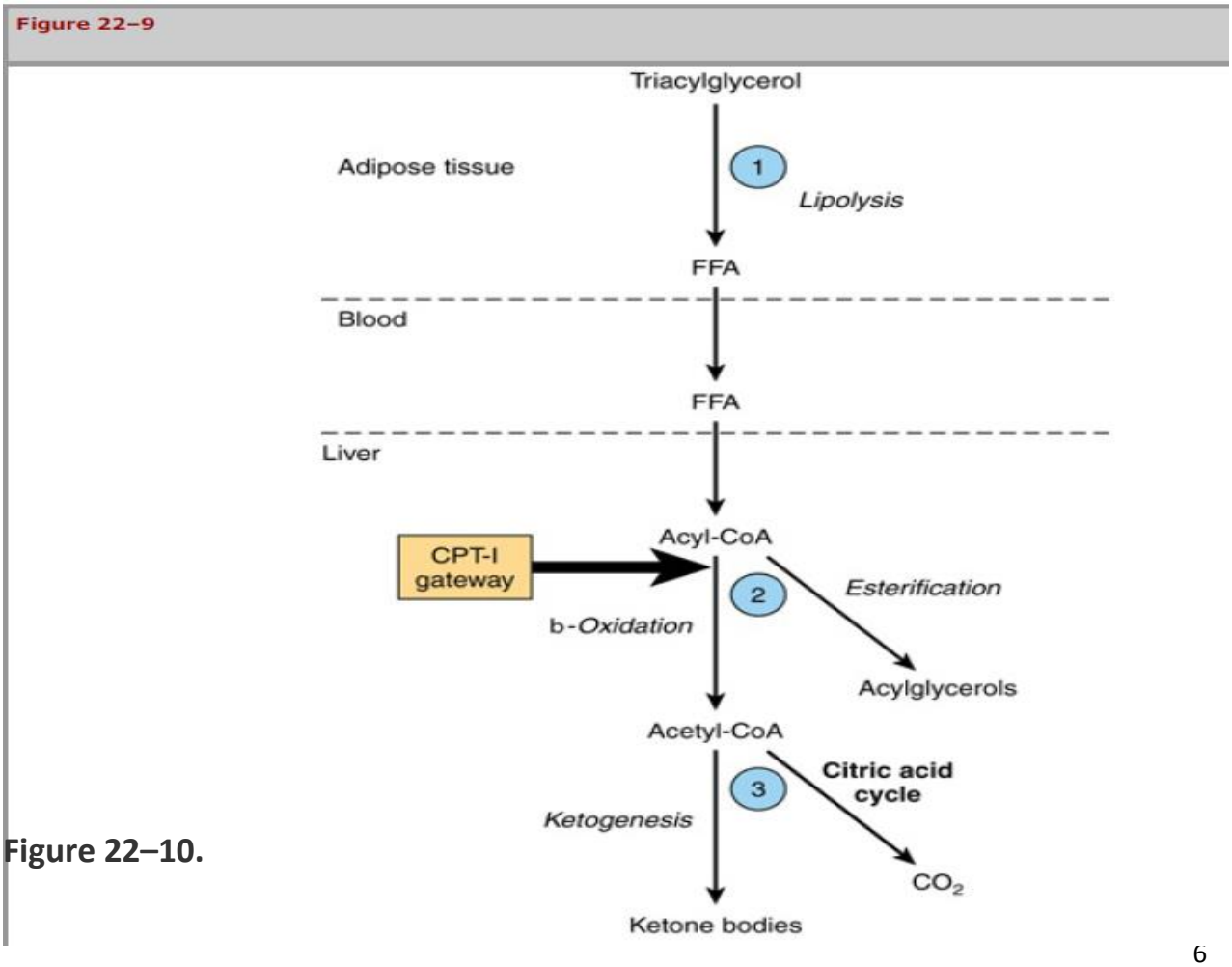
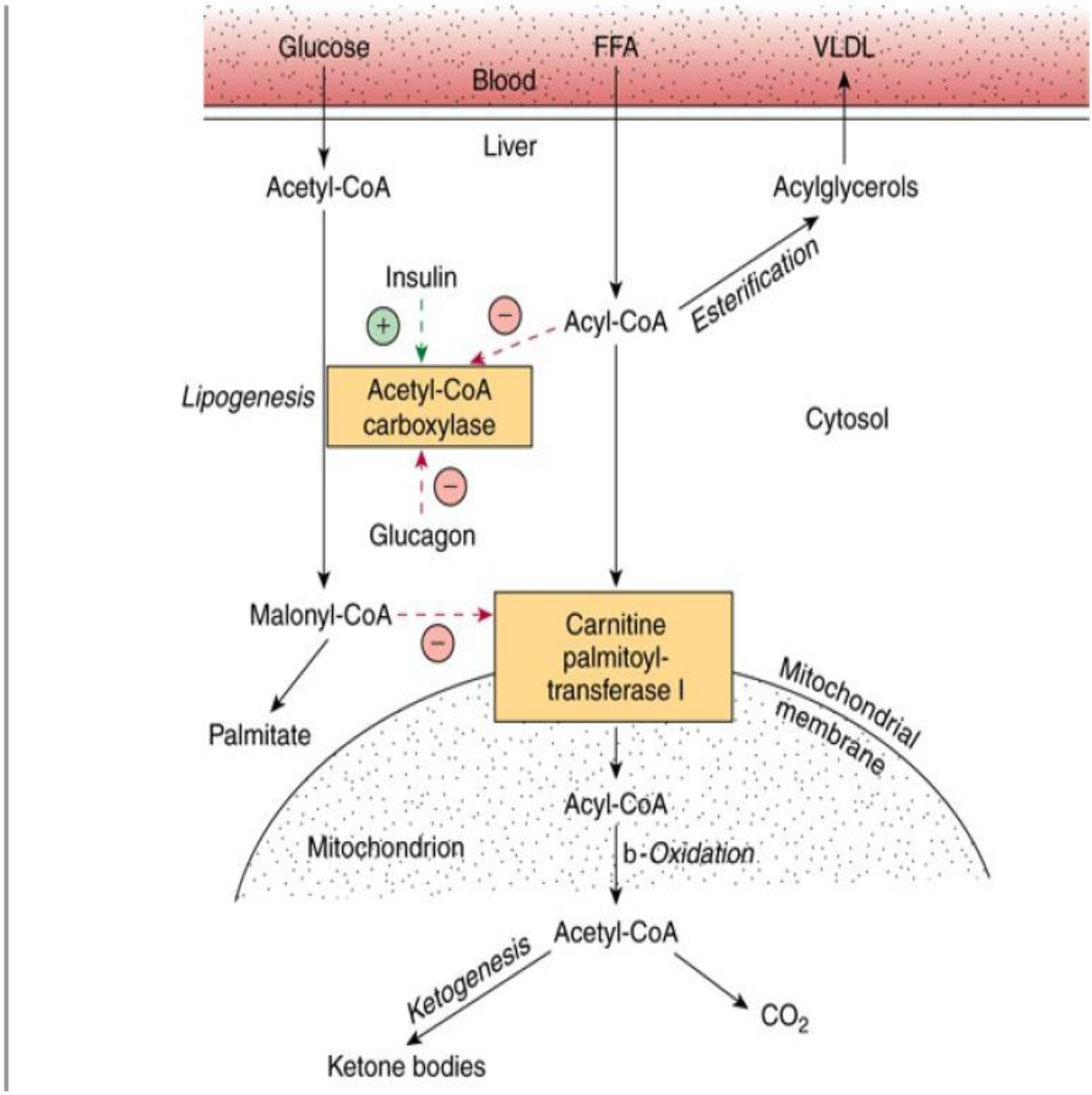


Figure 22–10.

A fall in the concentration of oxaloacetate, particularly within the mitochondria, can impair the ability of the citric acid cycle to metabolize acetyl-CoA and divert fatty acid oxidation toward ketogenesis. Such a fall may occur because of an increase in the (NADH)/(NAD+) ratio caused by increased β-oxidation of fatty acids affecting the equilibrium between oxaloacetate and malate, leading to a decrease in the concentration of oxaloacetate, and when gluconeogenesis is elevated, which occurs when blood glucose levels are low. The activation of pyruvate carboxylase, which catalyzes the conversion of pyruvate to oxaloacetate, by acetyl-CoA partially alleviates this problem, but in conditions such as starvation and untreated diabetes mellitus, ketone bodies are overproduced causing ketosis.



Metabolism of Acylglycerols & Sphingolipids

BIOMEDICAL IMPORTANCE

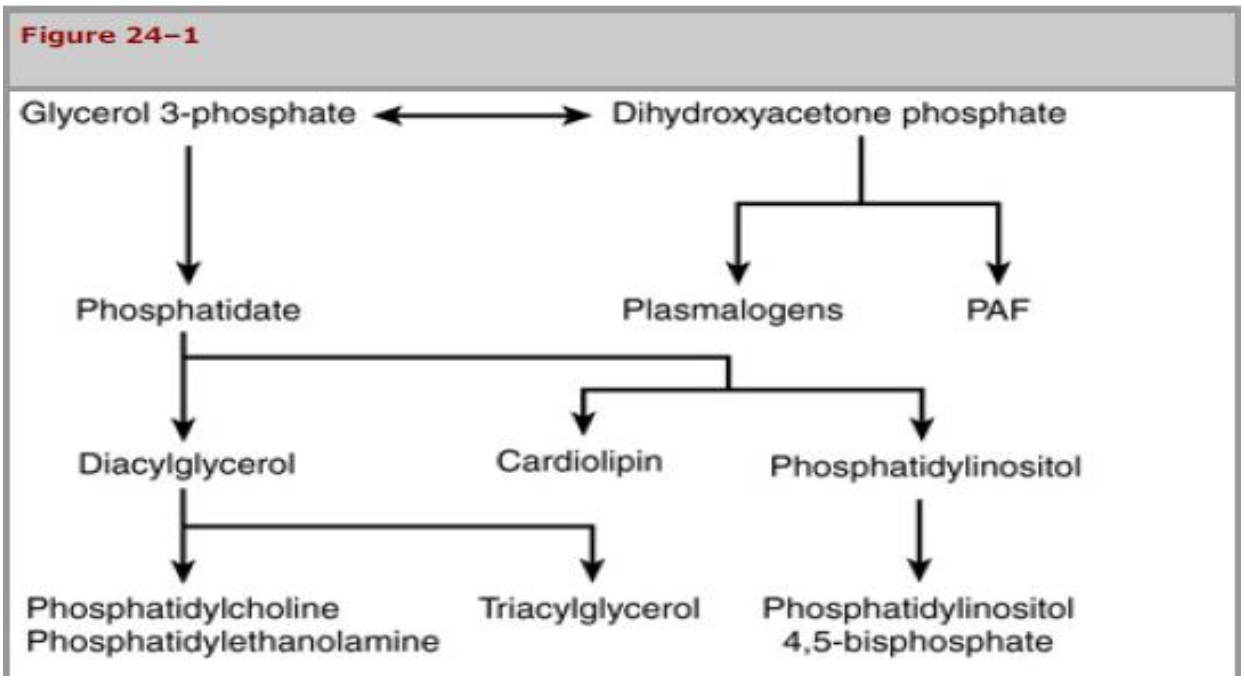
Acylglycerols constitute the majority of lipids in the body. Triacylglycerols are the major lipids in fat deposits and in food, and their roles in lipid transport and storage and in various diseases such as obesity, diabetes, and hyperlipoproteinemia will be described in subsequent chapters. The amphipathic nature of phospholipids and sphingolipids makes them ideally suitable as the main lipid component of cell membranes. Phospholipids also take part in the metabolism of many other lipids. Some phospholipids have specialized functions; eg, dipalmitoyl lecithin is a major component of **lung surfactant,** which is lacking in **respiratory distress syndrome** of the newborn. Inositol phospholipids in the cell membrane act as precursors of **hormone second messengers,** and **platelet-activating factor** is an alkylphospholipid. Glycosphingolipids, containing sphingosine and sugar residues as well as fatty acid that are found in the outer leaflet of the plasma membrane with their oligosaccharide chains facing outward, form part of the glycocalyx of the cell surface and are important (1) in cell adhesion and cell recognition, (2) as receptors for bacterial toxins (eg, the toxin that causes cholera), and (3) as ABO blood group substances. A dozen or so **glycolipid storage diseases** have been described (eg, Gaucher's disease and Tay-Sachs disease), each due to a genetic defect in the pathway for glycolipid degradation in the lysosomes.

HYDROLYSIS INITIATES CATABOLISM OF TRIACYLGLYCEROLS

Triacylglycerols must be hydrolyzed by a **lipase** to their constituent fatty acids and glycerol before further catabolism can proceed. Much of this hydrolysis (lipolysis) occurs in adipose tissue with release of free fatty acids into the plasma, where they are found combined with serum albumin . This is followed by free fatty acid uptake into tissues (including liver, heart, kidney, muscle, lung, testis, and adipose tissue, but not readily by brain), where they are oxidized or re-esterified. The utilization of glycerol depends upon whether such tissues have the enzyme **glycerol kinase,** which is found in significant amounts in liver, kidney, intestine, brown adipose tissue, and the lactating mammary gland.

TRIACYLGLYCEROLS & PHOSPHOGLYCEROLS ARE FORMED BY ACYLATION OF TRIOSE PHOSPHATES

The major pathways of triacylglycerol and phosphoglycerol biosynthesis are outlined in Figure 24–1. Important substances such as triacylglycerols, phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, and cardiolipin, a constituent of mitochondrial membranes, are formed from **glycerol-3-phosphate.** Significant branch points in the pathway occur at the phosphatidate and diacylglycerol steps. Phosphoglycerols containing an ether link (—C—O—C—), the best known of which are plasmalogens and platelet-activating factor (PAF), are derived from dihydroxyacetone phosphate. Glycerol 3-phosphate and dihydroxyacetone phosphate are intermediates in glycolysis, making a very important connection between carbohydrate and lipid metabolism.



Phosphatidate Is the Common Precursor in the Biosynthesis of Triacylglycerols, Many Phosphoglycerols, & Cardiolipin

Both glycerol and fatty acids must be activated by ATP before they can be incorporated into acylglycerols. **Glycerol kinase** catalyzes the activation of glycerol to *sn*-glycerol 3-phosphate.If the activity of this enzyme is absent or low, as in muscle or adipose tissue, most of the glycerol 3-phosphate is formed from

dihydroxyacetone phosphate by **glycerol-3-phosphate dehydrogenase** (Figure 24–2).

BIOSYNTHESIS OF TRIA CYLGLYCEROLS

Two molecules of acyl-CoA, formed by the activation of fatty acids by **acyl-CoA synthetase**, combine with glycerol 3-phosphate to form **phosphatidate** (1,2-diacylglycerol phosphate). This takes place in two stages, catalyzed by **glycerol-3-phosphate acyltransferase** and **1-acylglycerol-3-phosphate acyltransferase.** Phosphatidate is converted by **phosphatidate phosphohydrolase** and **diacylglycerol acyltransferase (DGAT)** to 1,2-diacylglycerol and then triacylglycerol. DGAT catalyzes the only step specific for triacylglycerol synthesis and is thought to be rate limiting in most circumstances. In intestinal mucosa, **monoacylglycerol acyltransferase** converts **monoacylglycerol** to 1,2-diacylglycerol in the **monoacylglycerol pathway.** Most of the activity of these enzymes resides in the endoplasmic reticulum, but some is found in mitochondria. Although phosphatidate phosphohydrolase protein is found mainly in the cytosol, the active form of the enzyme is membrane bound.

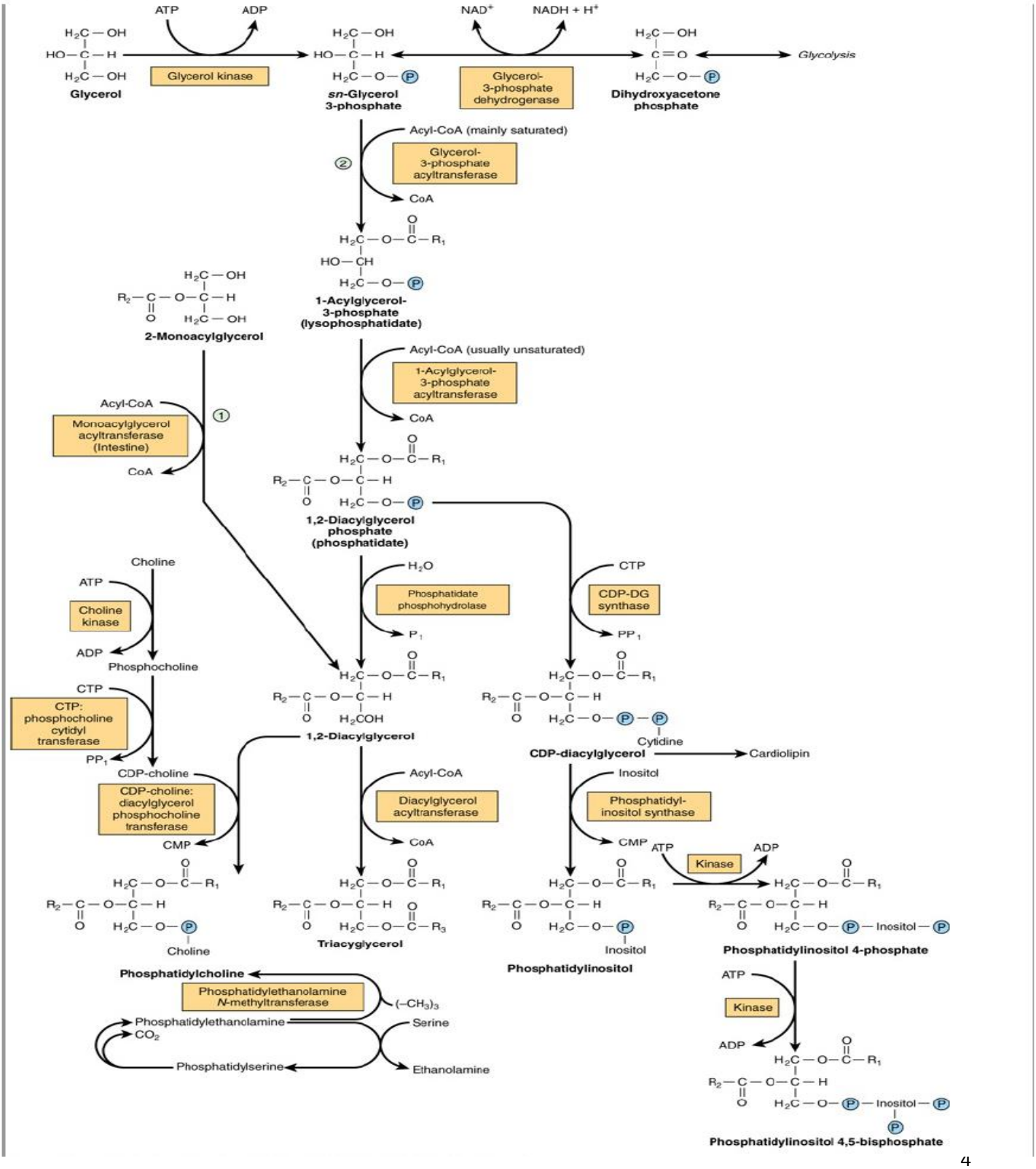
In the biosynthesis of phosphatidylcholine and phosphatidylethanolamine (Figure 24–2), choline or ethanolamine must first be activated by phosphorylation by ATP followed by linkage to CDP. The resulting CDP-choline or CDP-ethanolamine reacts with 1,2-diacylglycerol to form either phosphatidylcholine or phosphatidylethanolamine, respectively. Phosphatidylserine is formed from phosphatidylethanolamine directly by reaction with serine (Figure 24–2). Phosphatidylserine may re-form phosphatidylethanolamine by decarboxylation. An alternative pathway in liver enables phosphatidylethanolamine to give rise directly to phosphatidylcholine by progressive methylation of the ethanolamine residue. In spite of these sources of choline, it is considered to be an essential nutrient in many mammalian species, although this has not been established in humans.

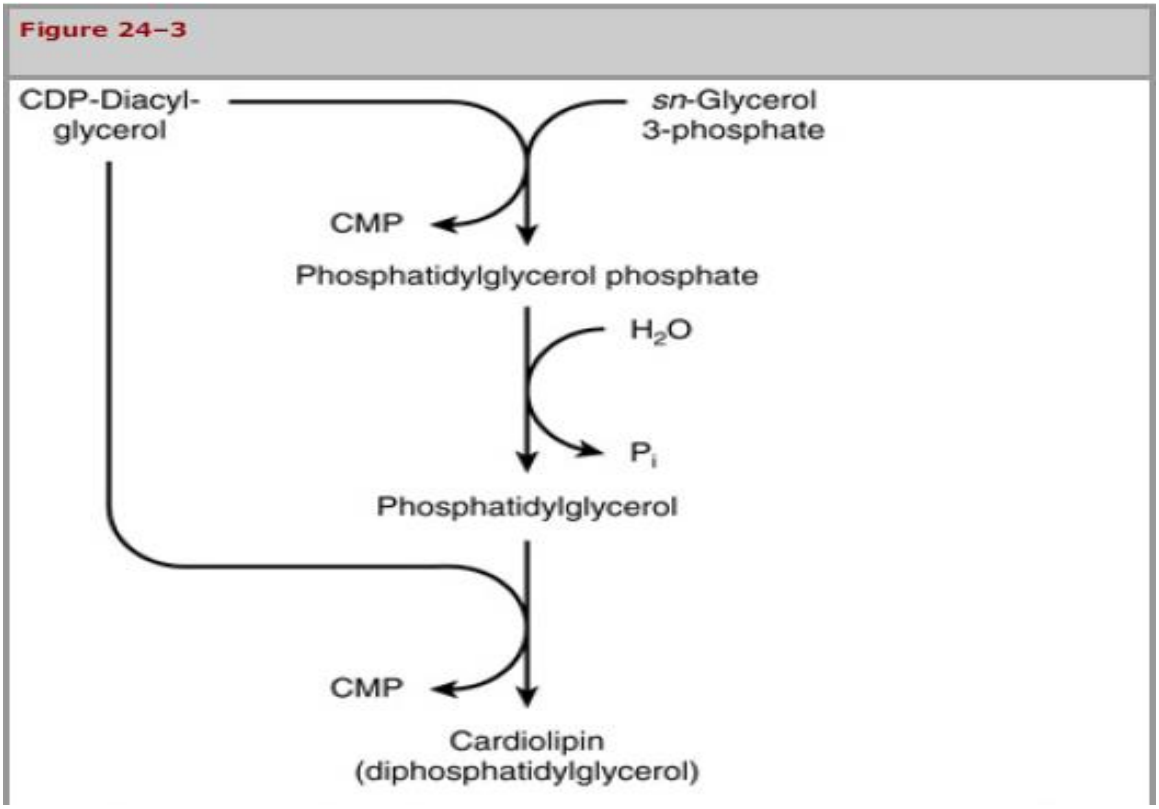
The regulation of triacylglycerol, phosphatidylcholine, and phosphatidylethanolamine biosynthesis is driven by the availability of free fatty acids. Those that escape oxidation are preferentially converted to phospholipids, and when this requirement is satisfied they are used for triacylglycerol synthesis.

Cardiolipin (diphosphatidylglycerol; Figure 15–10) is a phospholipid present in mitochondria. It is formed from phosphatidylglycerol, which in turn is synthesized from CDP-diacylglycerol (Figure 24–2) and glycerol 3-phosphate according to the scheme shown in Figure 24–3. Cardiolipin, found in the inner membrane of

mitochondria, has a key role in mitochondrial structure and function, and is also thought to be involved in programmed cell death (**apoptosis**).

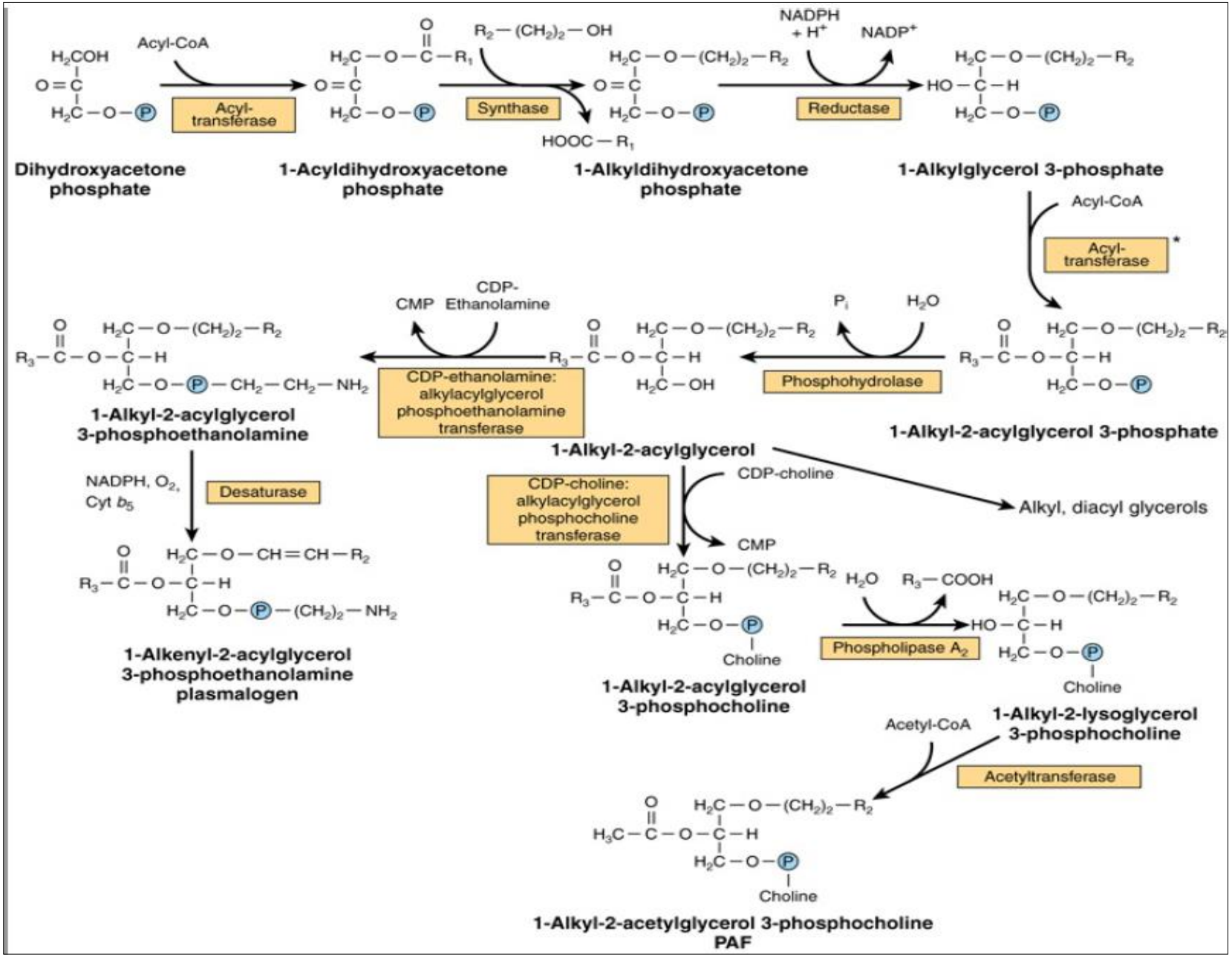
Figure 24-2.





BIOSYNTHESIS OF GLYCEROL ETHER PHOSPHOLIPIDS

This pathway is located in peroxisomes. Dihydroxyacetone phosphate is the precursor of the glycerol moiety of glycerol ether phospholipids (Figure 24–4). This compound combines with acyl-CoA to give 1-acyldihydroxyacetone phosphate. The ether link is formed in the next reaction, producing 1-alkyldihydroxyacetone phosphate, which is then converted to 1-alkylglycerol 3-phosphate. After further acylation in the 2 position, the resulting 1-alkyl-2-acylglycerol 3-phosphate (analogous to phosphatidate in Figure 24–2) is hydrolyzed to give the free glycerol derivative. **Plasmalogens,** which comprise much of the phospholipid in mitochondria, are formed by desaturation of the analogous 3-phosphoethanolamine derivative (Figure 24–4). **Platelet-activating factor (PAF)** (1-alkyl-2-acetyl-*sn*-glycerol-3-phosphocholine) is synthesized from the corresponding 3-phosphocholine derivative. It is formed by many blood cells and other tissues and aggregates platelets at concentrations as low as 10–11 mol/L. It also has hypotensive and ulcerogenic properties and is involved in a variety of biologic responses, including inflammation, chemotaxis, and protein phosphorylation.

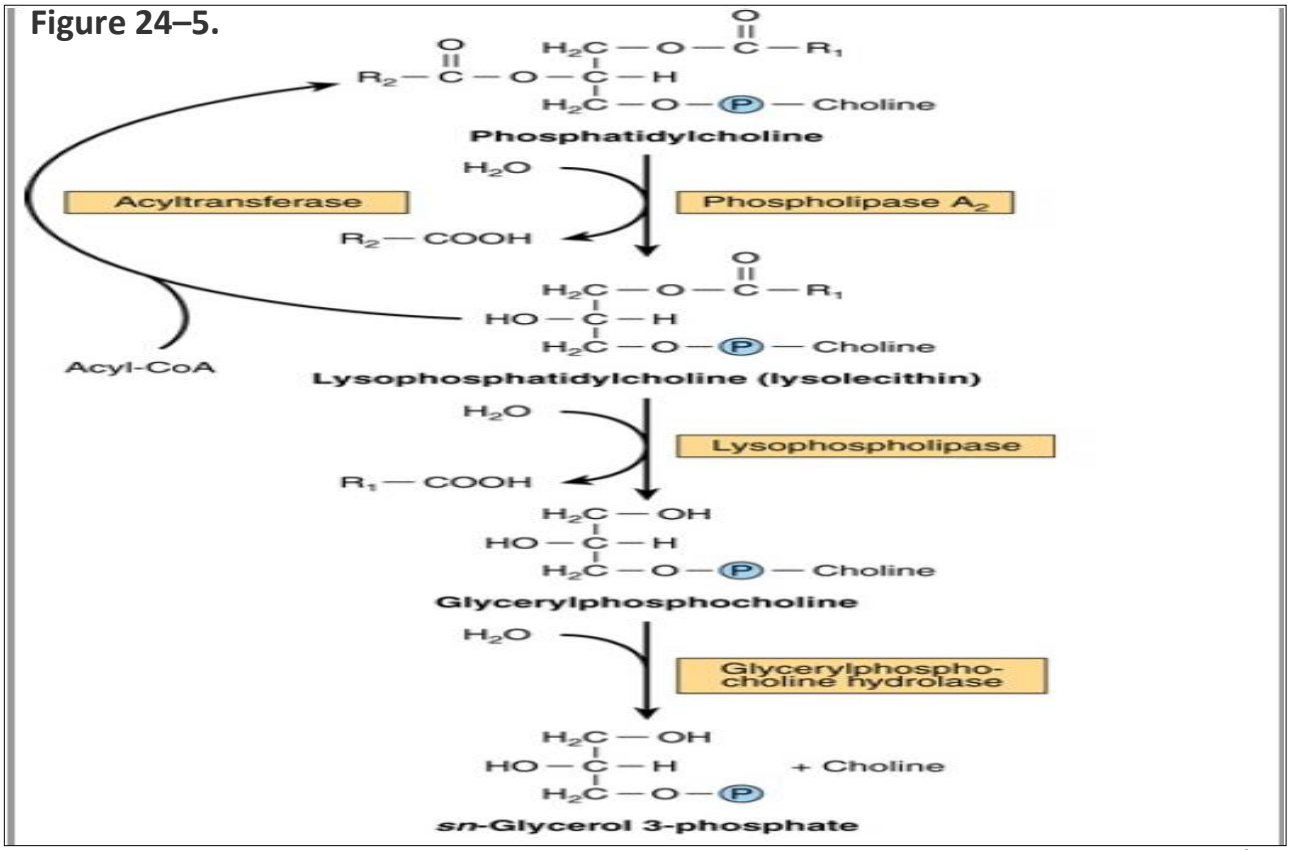

Acyl-CoA
Acyl-transferase
Dihydroxyacetone phosphate
1-Acyldihydroxyacetone phosphate
Synthase
HOOC — R1
NADPH + H+
NADP+
Reductase
1-Alkyldihydroxyacetone phosphate
1-Alkylglycerol 3-phosphate
Acyl-CoA
Acyl-transferase
1-Alkyl-2-acylglycerol 3-phosphate
Pi
H2O
Phosphohydrolase
1-Alkyl-2-acylglycerol
CDP-choline
Alkyl, diacyl glycerols
CDP-choline: alkylacylglycerol phosphocholine transferase
CMP
1-Alkyl-2-acylglycerol 3-phosphocholine
Choline
H2O
R3 — COOH
Phospholipase A2
1-Alkyl-2-lysoglycerol 3-phosphocholine
Choline
Acetyl-CoA
Acetyltransferase
1-Alkyl-2-acetylglycerol 3-phosphocholine
PAF
CDP-Ethanolamine
CMP
CDP-ethanolamine: alkylacylglycerol phosphoethanolamine transferase
1-Alkyl-2-acylglycerol 3-phosphoethanolamine
NADPH, O2, Cyt b5
Desaturase
1-Alkenyl-2-acylglycerol 3-phosphoethanolamine plasmalogen

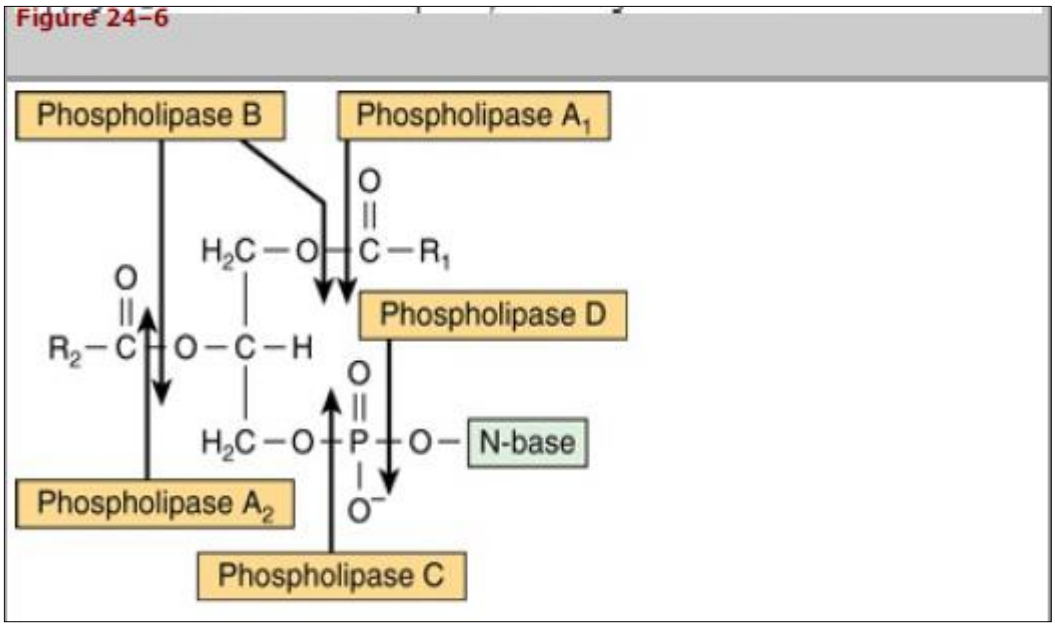
Metabolism of Acylglycerols & Sphingolipids

Phospholipases Allow Degradation & Remodeling of Phosphoglycerols

Although phospholipids are actively degraded, each portion of the molecule turns over at a different rate—eg, the turnover time of the phosphate group is different from that of the 1-acyl group. This is due to the presence of enzymes that allow partial degradation followed by resynthesis (Figure 24–5). **Phospholipase A**2 catalyzes the hydrolysis of glycerophospholipids to form a free fatty acid and lysophospholipid, which in turn may be reacylated by acyl-CoA in the presence of an acyltransferase. Alternatively, lysophospholipid (eg, lysolecithin) is attacked by **lysophospholipase,** forming the corresponding glyceryl phosphoryl base, which may then be split by a hydrolase liberating glycerol 3-phosphate plus base.
Phospholipases A1, A2, B, C, and D attack the bonds indicated in Figure 24–6. **Phospholipase A**2 is found in pancreatic fluid and snake venom as well as in many types of cells; **phospholipase C** is one of the major toxins secreted by bacteria; and **phospholipase D** is known to be involved in mammalian signal transduction.

Figure 24–5.



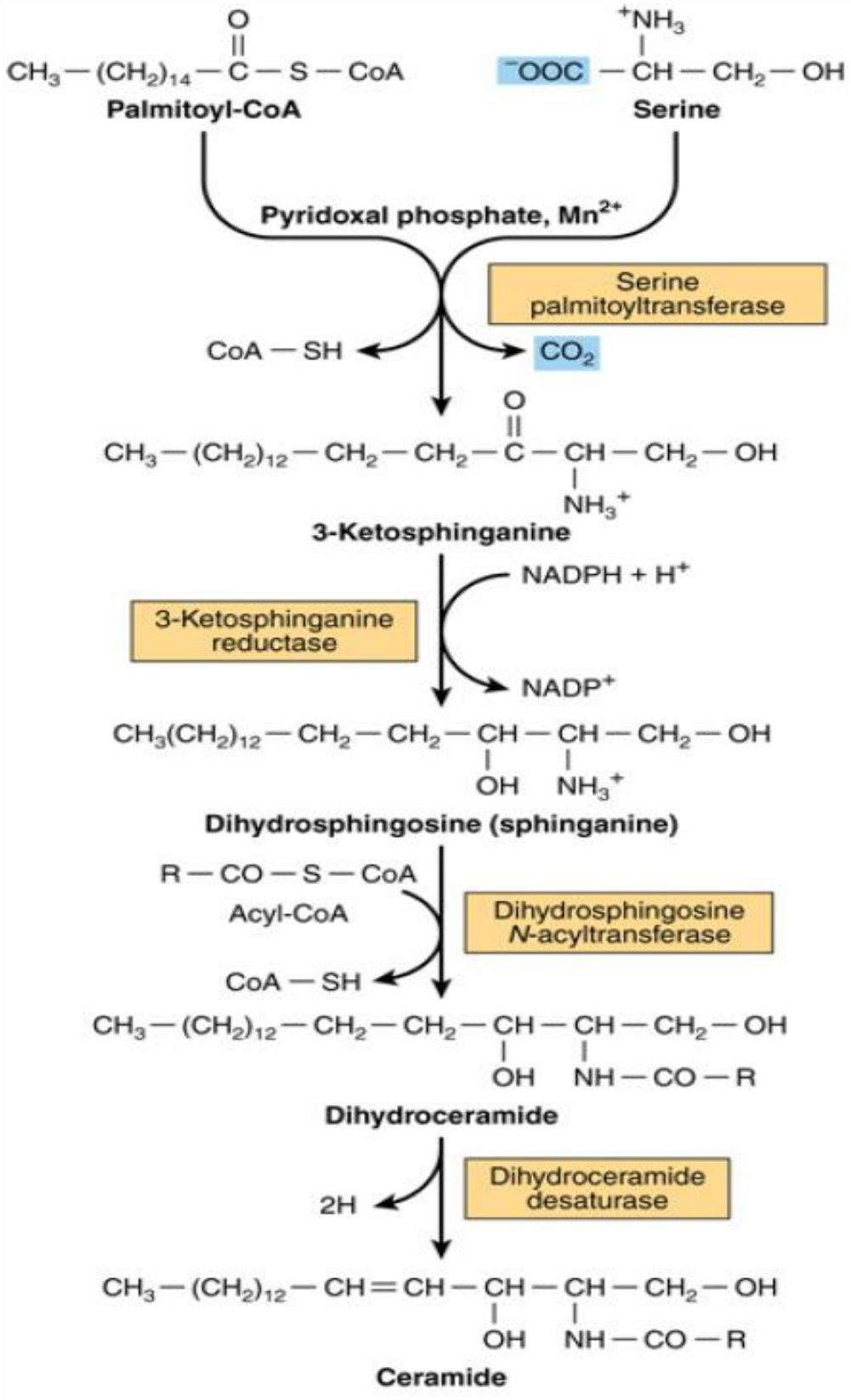


Lysolecithin (lysophosphatidylcholine) may be formed by an alternative route that involves **lecithin: cholesterol acyltransferase (LCAT).** This enzyme, found in plasma, catalyzes the transfer of a fatty acid residue from the 2 position of lecithin to cholesterol to form cholesteryl ester and lysolecithin, and is considered to be responsible for much of the cholesteryl ester in plasma lipoproteins. Long-chain saturated fatty acids are found predominantly in the 1 position of phospholipids, whereas the polyunsaturated fatty acids (eg, the precursors of prostaglandins) are incorporated more frequently into the 2 position. The incorporation of fatty acids into lecithin occurs in three ways; by complete synthesis of the phospholipid; by transacylation between cholesteryl ester and lysolecithin; and by direct acylation of lysolecithin by acyl-CoA. Thus, a continuous exchange of the fatty acids is possible, particularly with regard to introducing essential fatty acids into phospholipid molecules.

ALL SPHINGOLIPIDS ARE FORMED FROM CERAMIDE

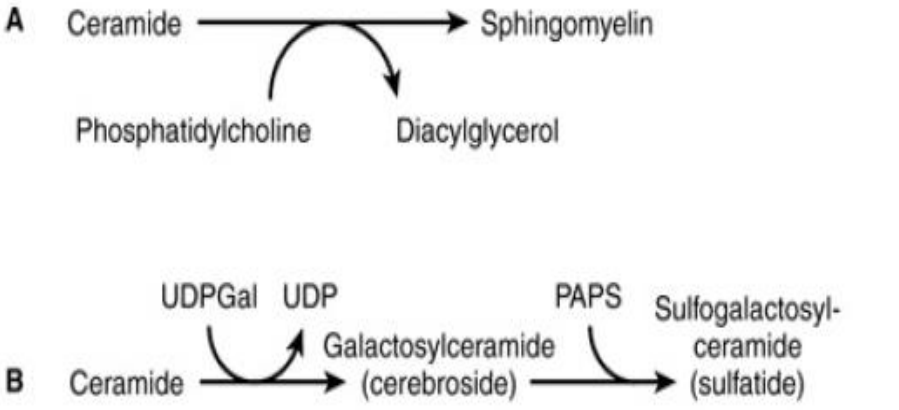
Ceramide is synthesized in the endoplasmic reticulum from the amino acid serine as shown in Figure 24–7. Ceramide is an important signaling molecule (second messenger) regulating pathways including programmed cell death **(apoptosis),** the **cell cycle,** and **cell differentiation and senescence.**

Figure 24–7


Palmitoyl-CoA
Serine
Pyridoxal phosphate, Mn2+
Serine palmitoyltransferase
CoA — SH
CO2
3-Ketosphinganine
NADPH + H+
3-Ketosphinganine reductase
NADP+
Dihydrosphingosine (sphinganine)
R — CO — S — CoA
Acyl-CoA
Dihydrosphingosine N-acyltransferase
CoA — SH
Dihydroceramide
2H
Dihydroceramide desaturase
Ceramide

Sphingomyelins are phospholipids and are formed when ceramide reacts with phosphatidylcholine to form sphingomyelin plus diacylglycerol (Figure 24–8A). This occurs mainly in the Golgi apparatus and to a lesser extent in the plasma membrane.

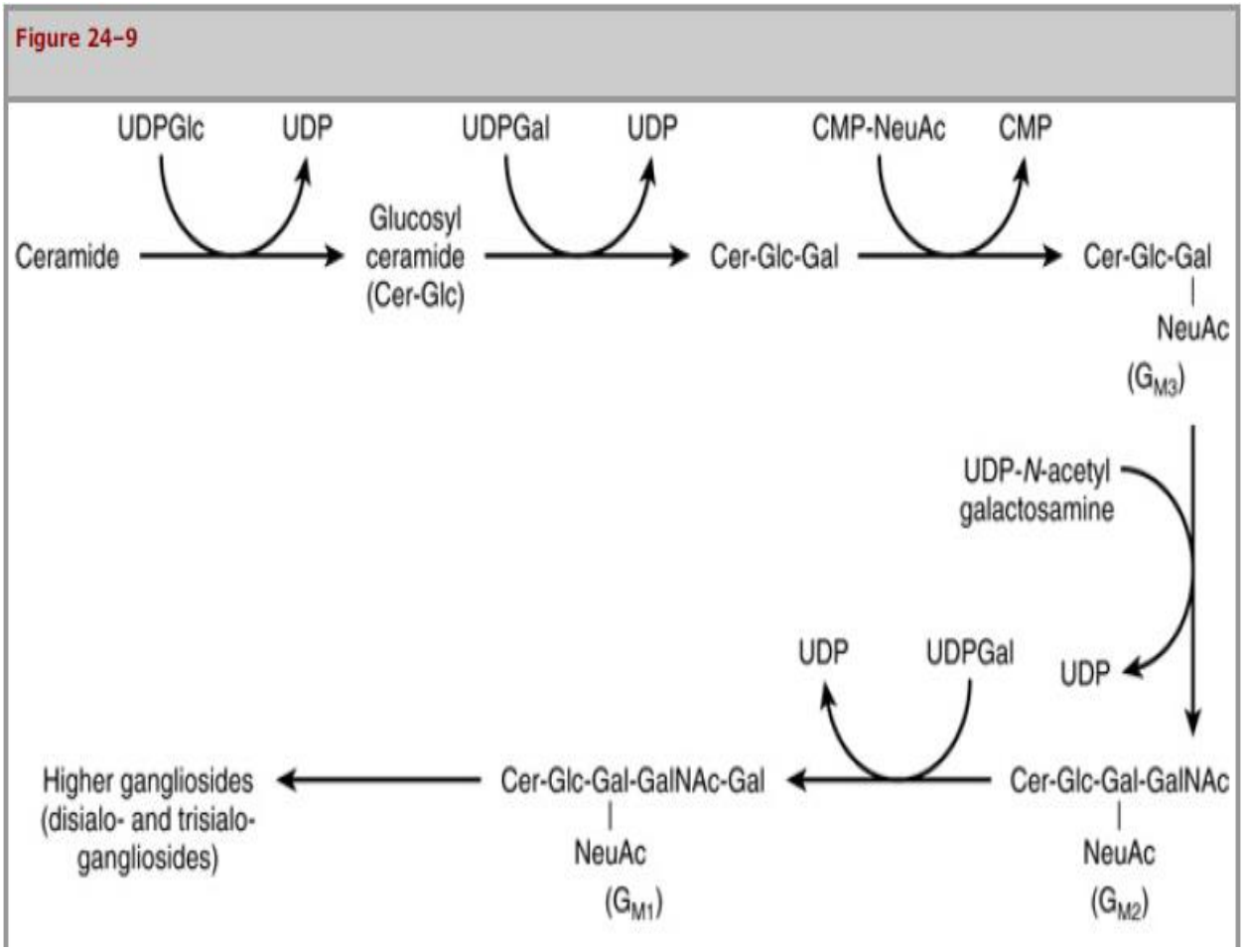
Figure 24–8.



Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA: *Harper's Illustrated Biochemistry, 29th Edition*: www.accessmedicine.com

Glycosphingolipids Are a Combination of Ceramide with One or More Sugar Residues

The simplest glycosphingolipids **(cerebrosides)** are **galactosylceramide (GalCer)** and **glucosylceramide (GlcCer).** GalCer is a major lipid of **myelin,** whereas GlcCer is the major glycosphingolipid of **extraneural tissues** and a precursor of most of the more complex glycosphingolipids. GalCer (Figure 24–8B) is formed in a reaction between ceramide and UDPGal (formed by epimerization from UDPGlc).
Sulfogalactosylceramide and other sulfolipids such as the **sulfo(galacto)-glycerolipids** and the **steroid sulfates** are formed after further reactions involving 3'- phosphoadenosine-5'-phosphosulfate (PAPS; "active sulfate"). **Gangliosides** are synthesized from ceramide by the stepwise addition of activated sugars (eg, UDPGlc and UDPGal) and a **sialic acid,** usually *N*-acetylneuraminic acid (Figure 24–9). A large number of gangliosides of increasing molecular weight may be formed. Most of the enzymes transferring sugars from nucleotide sugars (glycosyl transferases) are found in the Golgi apparatus.



Glycosphingolipids are constituents of the outer leaflet of plasma membranes and are important in **cell adhesion** and **cell recognition.** Some are antigens, eg, ABO blood group substances. Certain gangliosides function as receptors for bacterial toxins (eg, for **cholera toxin,** which subsequently activates adenylyl cyclase).

Lipid Transport & Storage

BIOMEDICAL IMPORTANCE

Fat absorbed from the diet and lipids synthesized by the liver and adipose tissue must be transported between the various tissues and organs for utilization and storage. Since lipids are insoluble in water, the problem of how to transport them in the aqueous blood plasma is solved by associating nonpolar lipids (triacylglycerol and cholesteryl esters) with amphipathic lipids (phospholipids and cholesterol) and proteins to make water-miscible lipoproteins.

In a meal-eating omnivore such as the human, excess calories are ingested in the anabolic phase of the feeding cycle, followed by a period of negative caloric balance when the organism draws upon its carbohydrate and fat stores. Lipoproteins mediate this cycle by transporting lipids from the intestines as chylomicrons—and from the liver as very low density lipoproteins (VLDL)—to most tissues for oxidation and to adipose tissue for storage. Lipid is mobilized from adipose tissue as free fatty acids (FFA) bound to serum albumin.

Abnormalities of lipoprotein metabolism cause various **hypo-** or **hyperlipoproteinemias.** The most common of these is in **diabetes mellitus,** where insulin deficiency causes excessive mobilization of FFA and underutilization of chylomicrons and VLDL, leading to **hypertriacylglycerolemia.** Most other pathologic conditions affecting lipid transport are due primarily to inherited defects, some of which cause **hypercholesterolemia** and premature **atherosclerosis (Table 26–1). Obesity**—particularly abdominal obesity—is a risk factor for increased mortality, hypertension, type 2 diabetes mellitus, hyperlipidemia, hyperglycemia, and various endocrine dysfunctions.

LIPIDS ARE TRANSPORTED IN THE PLASMA AS LIPOPROTEINS

Four Major Lipid Classes Are Present in Lipoproteins

Plasma lipids consist of **triacylglycerols** (16%), **phospholipids** (30%), **cholesterol** (14%), and **cholesteryl esters** (36%) and a much smaller fraction of unesterified long-chain fatty acids (free fatty acids or FFA) (4%). This latter fraction, the **FFA,** is metabolically the most active of the plasma lipids.

Four Major Groups of Plasma Lipoproteins Have Been Identified

Since fat is less dense than water, the density of a lipoprotein decreases as the proportion of lipid to protein increases (Table 25–1). Four major groups of lipoproteins have been identified that are important physiologically and in clinical diagnosis. These are (1) **chylomicrons,** derived from intestinal absorption of triacylglycerol and other lipids; (2) **very low density lipoproteins** (VLDL, or pre-β -lipoproteins), derived from the liver for the export of triacylglycerol; (3) **low-density lipoproteins** (LDL, or β-lipoproteins), representing a final stage in the catabolism of VLDL; and (4) **high-density lipoproteins** (HDL, or α-lipoproteins), involved in cholesterol transport and also in VLDL and chylomicron metabolism.
Triacylglycerol is the predominant lipid in chylomicrons and VLDL, whereas cholesterol and phospholipid are the predominant lipids in LDL and HDL, respectively (Table 25–1).
Lipoproteins may be separated according to their electrophoretic properties intoα **-,β -,** and **pre-β -lipoproteins.**

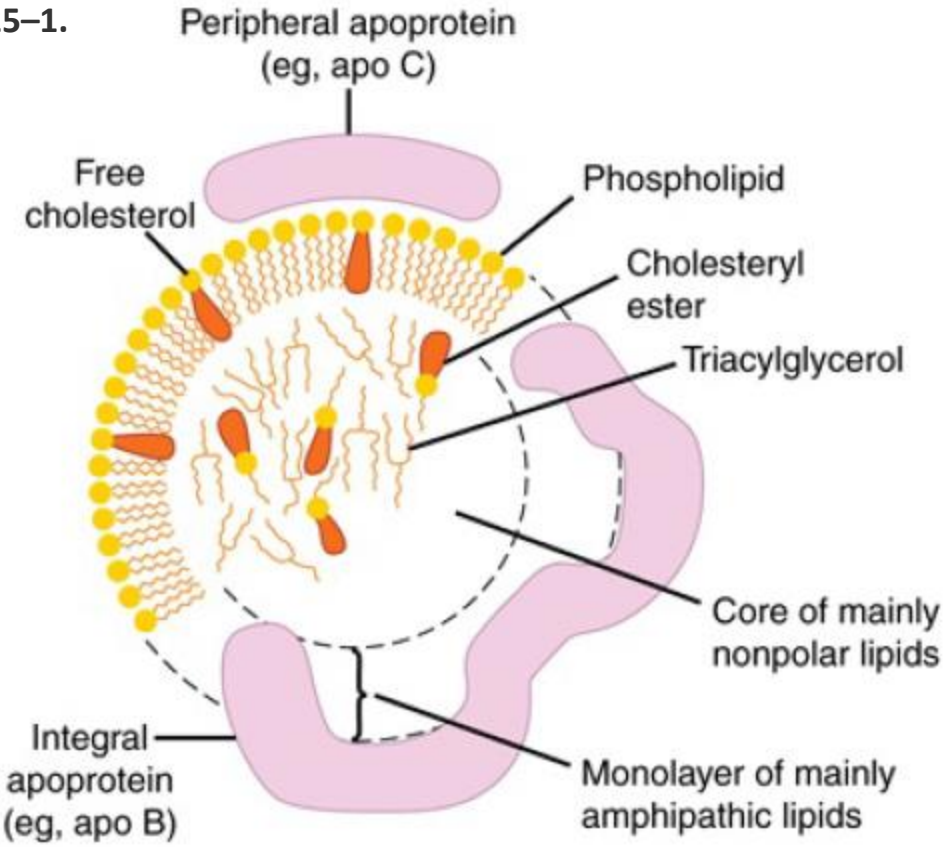
Table 25–1 Composition of the Lipoproteins in Plasma of Humans

				Composition			
Lipoprotein	**Source**	**Diameter (nm)**	**Density (g/mL)**	**Protein (%)**	**Lipid (%)**	**Main Lipid Components**	**Apolipoproteins**
Chylomicrons	Intestine	90–1000	< 0.95	1–2	98–99	Triacylglycerol	A-I, A-II, A-IV,[1] B-48, C-I, C-II, C-III, E
Chylomicron remnants	Chylomicrons	45–150	< 1.006	6–8	92–94	Triacylglycerol, phospholipids, cholesterol	B-48, E
VLDL	Liver (intestine)	30–90	0.95–1.006	7–10	90–93	Triacylglycerol	B-100, C-I, C-II, C-III
IDL	VLDL	25–35	1.006–1.019	11	89	Triacylglycerol, cholesterol	B-100, E
LDL	VLDL	20–25	1.019–1.063	21	79	Cholesterol	B-100
HDL	Liver, intestine, VLDL, chylomicrons					Phospholipids, cholesterol	A-I, A-II, A-IV, C-I, C-II, C-III, D,[2] E
HDL_1		20–25	1.019–1.063	32	68		
HDL_2		10–20	1.063–1.125	33	67		
HDL^3		5–10	1.125–1.210	57	43		
Pre -HDL^3		< 5	> 1.210				A-I
Albumin/free fatty acids	Adipose tissue		> 1.281	99	1	Free fatty acids	

Lipoproteins Consist of a Nonpolar Core & a Single Surface Layer of Amphipathic Lipids

The **nonpolar lipid core** consists of mainly **triacylglycerol** and **cholesteryl ester** and is surrounded by a **single surface layer** of **amphipathic phospholipid** and **cholesterol** molecules (Figure 25–1). These are oriented so that their polar groups face outward to the aqueous medium, as in the cell membrane (Chapter 15). The protein moiety of a lipoprotein is known as an **apolipoprotein** or **apoprotein,** constituting nearly 70% of some HDL and as little as 1% of chylomicrons. Some apolipoproteins are integral and cannot be removed, whereas others are free to transfer to other lipoproteins.

Figure 25–1.



The Distribution of Apolipoproteins Characterizes the Lipoprotein

One or more apolipoproteins (proteins or polypeptides) are present in each lipoprotein. The major apolipoproteins of HDL (α-lipoprotein) are designated A (Table 25–1). The main apolipoprotein of LDL (β-lipoprotein) is apolipoprotein B (B-100), which is found also in VLDL. Chylomicrons contain a truncated form of apo B (B-48) that is synthesized in the intestine, while B-100 is synthesized in the liver. Apo C-I, C-II, and C-III are smaller polypeptides (molecular mass 7000–9000 Da) freely transferable between several different lipoproteins. Apo E, found in VLDL, HDL, chylomicrons, and chylomicron remnants, is also freely transferable; it accounts for 5–10% of total VLDL apolipoproteins in normal subjects.
Apolipoproteins carry out several roles: (1) they can form part of the structure of the lipoprotein, eg, apo B; (2) they are enzyme cofactors, eg, C-II for lipoprotein lipase, A-I for lecithin:cholesterol acyltransferase, or enzyme inhibitors, eg, apo A-II and apo C-III for lipoprotein lipase, apo C-I for cholesteryl ester transfer protein; and (3) they act as ligands for interaction with lipoprotein receptors in tissues, eg, apo B-100 and apo E for the LDL receptor, apo E for the LDL-receptor-related protein (LRP), which has been identified as the remnant receptor, and apo A-I for the HDL receptor.

TRIACYLGLYCEROL IS TRANSPORTED FROM THE INTESTINES IN CHYLOMICRONS & FROM THE LIVER IN VERY LOW DENSITY LIPOPROTEINS

By definition, **chylomicrons** are found in **chyle** formed only by the lymphatic system **draining the intestine.** They are responsible for the transport of all dietary lipids into the circulation. Small quantities of VLDL are also to be found in chyle; however, most **VLDL in the plasma** are of hepatic origin. **They are the vehicles of transport of triacylglycerol from the liver to the extrahepatic tissues.**
Newly secreted or "nascent" chylomicrons and VLDL contain only a small amount of apolipoproteins C and E, and the full complement is acquired from HDL in the circulation (Figures 25–3 and 25–4). Apo B, however, is an integral part of the lipoprotein particles, it is incorporated inside the cells and is essential for chylomicron and VLDL formation.In **abetalipoproteinemia** (a rare disease), lipoproteins containing apo B are not formed and lipid droplets accumulate in the intestine and liver.

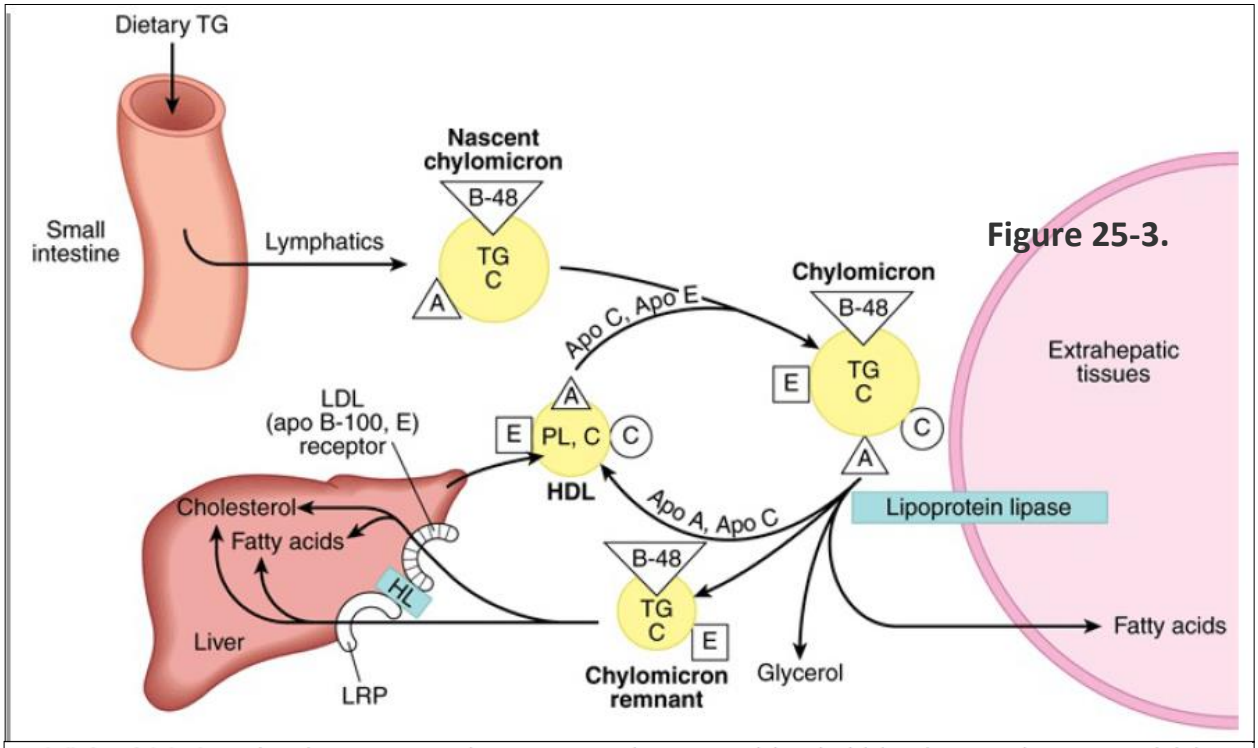
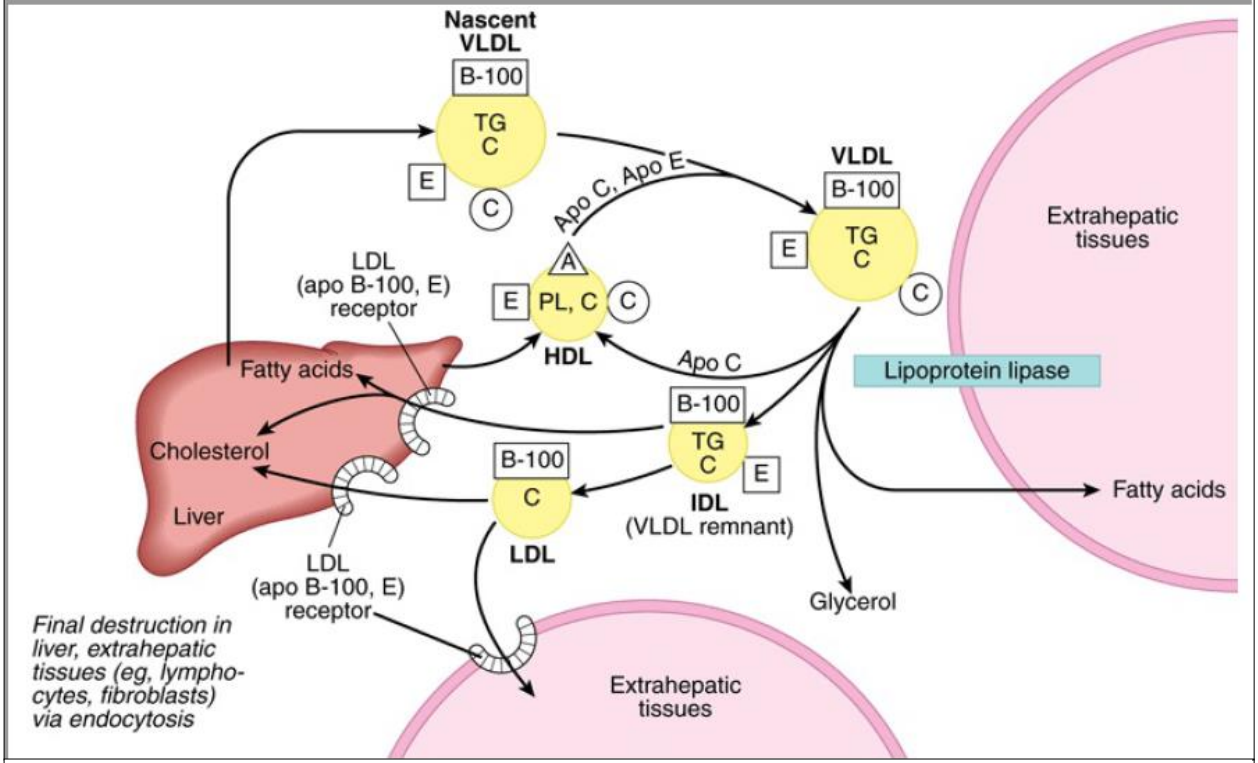


Figure 25-3.

Metabolic fate of chylomicrons. (A, apolipoprotein A; B-48, apolipoprotein B-48; C, apolipoprotein C; C, cholesterol and cholesteryl ester; E, apolipoprotein E; HDL, high-density lipoprotein; HL, hepatic lipase; LRP, LDL-receptor-related protein; PL, phospholipid; TG, triacylglycerol.) Only the predominant lipids are shown.

Figure 25–4



Metabolic fate of very low density lipoproteins (VLDL) and production of low-density lipoproteins (LDL). (A, apolipoprotein A; B-100, apolipoprotein B-100; C, apolipoprotein C; C, cholesterol and cholesteryl ester; E, apolipoprotein E; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; PL, phospholipid; TG, triacylglycerol.) Only the predominant lipids are shown. It is possible that some IDL is also metabolized via the low density lipoproten receptor-related protein (LRP.)

CHYLOMICRONS & VERY LOW DENSITY LIPOPROTEINS ARE RAPIDLY CATABOLIZED

The clearance of chylomicrons from the blood is rapid, the half-time of disappearance being under 1 h in humans. Larger particles are catabolized more quickly than smaller ones. Fatty acids originating from chylomicron triacylglycerol are delivered mainly to adipose tissue, heart, and muscle (80%), while ~20% goes to the liver. However, **the liver does not metabolize native chylomicrons or VLDL significantly;** thus, the fatty acids in the liver must be secondary to their metabolism in extrahepatic tissues.

Triacylglycerols of Chylomicrons & VLDL Are Hydrolyzed by Lipoprotein Lipase

Lipoprotein lipase is located on the walls of blood capillaries, anchored to the endothelium by negatively charged proteoglycan chains of heparan sulfate. It has been found in heart, adipose tissue, spleen, lung, renal medulla, aorta, diaphragm, and lactating mammary gland, although it is not active in adult liver. It is not normally found in blood; however, following injection of **heparin,** lipoprotein lipase is released from its heparan sulfate binding sites into the circulation. **Hepatic lipase** is bound to the sinusoidal surface of liver cells and is also released by heparin. This enzyme, however, does not react readily with chylomicrons or VLDL but is involved in chylomicron remnant and HDL metabolism.

Both **phospholipids** and **apo C-II** are required as cofactors for lipoprotein lipase activity, while **apo A-II and apo C-III** act as inhibitors. Hydrolysis takes place while the lipoproteins are attached to the enzyme on the endothelium. Triacylglycerol is hydrolyzed progressively through a diacylglycerol to a monoacylglycerol and finally to FFA plus glycerol. Some of the released FFA return to the circulation, attached to albumin, but the bulk is transported into the tissue (Figures 25–3 and 25–4). Heart lipoprotein lipase has a low *K*m for triacylglycerol, about one-tenth of that for the enzyme in adipose tissue. This enables the delivery of fatty acids from triacylglycerol to be **redirected from adipose tissue to the heart in the starved state** when the plasma triacylglycerol decreases. A similar redirection to the mammary gland occurs during lactation, allowing uptake of lipoprotein triacylglycerol fatty acid for **milk fat** synthesis. The **VLDL receptor** plays an

important part in the delivery of fatty acids from VLDL triacylglycerol to adipocytes by binding VLDL and bringing it into close contact with lipoprotein lipase. In adipose tissue, **insulin** enhances lipoprotein lipase synthesis in adipocytes and its translocation to the luminal surface of the capillary endothelium.

The Action of Lipoprotein Lipase Forms Remnant Lipoproteins

Reaction with lipoprotein lipase results in the loss of 70–90% of the triacylglycerol of chylomicrons and in the loss of apo C (which returns to HDL) but not apo E, which is retained. The resulting **chylomicron remnant** is about half the diameter of the parent chylomicron and is relatively enriched in cholesterol and cholesteryl esters because of the loss of triacylglycerol (Figure 25–3). Similar changes occur to VLDL, with the formation of **VLDL remnants** (also called **intermediate-density lipoprotein (IDL**) (Figure 25–4).

The Liver Is Responsible for the Uptake of Remnant Lipoproteins

Chylomicron remnants are taken up by the liver by receptor-mediated endocytosis, and the cholesteryl esters and triacylglycerols are hydrolyzed and metabolized. Uptake is mediated by **apo E** (Figure 25–3), via two apo E-dependent receptors, the **LDL (apo B-100, E) receptor** and the **LRP (LDL receptor-related protein).** Hepatic lipase has a dual role: (1) it acts as a ligand to facilitate remnant uptake and (2) it hydrolyzes remnant triacylglycerol and phospholipid.
After metabolism to IDL, VLDL may be taken up by the liver directly via the LDL (apo B-100, E) receptor, or it may be converted to LDL. Only one molecule of apo B-100 is present in each of these lipoprotein particles, and this is conserved during the transformations. Thus, each LDL particle is derived from a single precursor VLDL particle (Figure 25–4). In humans, a relatively large proportion of IDL forms LDL, accounting for the increased concentrations of LDL in humans compared with many other mammals.

LDL IS METABOLIZED VIA THE LDL RECEPTOR

The liver and many extrahepatic tissues express the **LDL (apo B-100, E) receptor.** It is so designated because it is specific for apo B-100 but not B-48, which lacks the carboxyl terminal domain of B-100 containing the LDL receptor ligand, and it

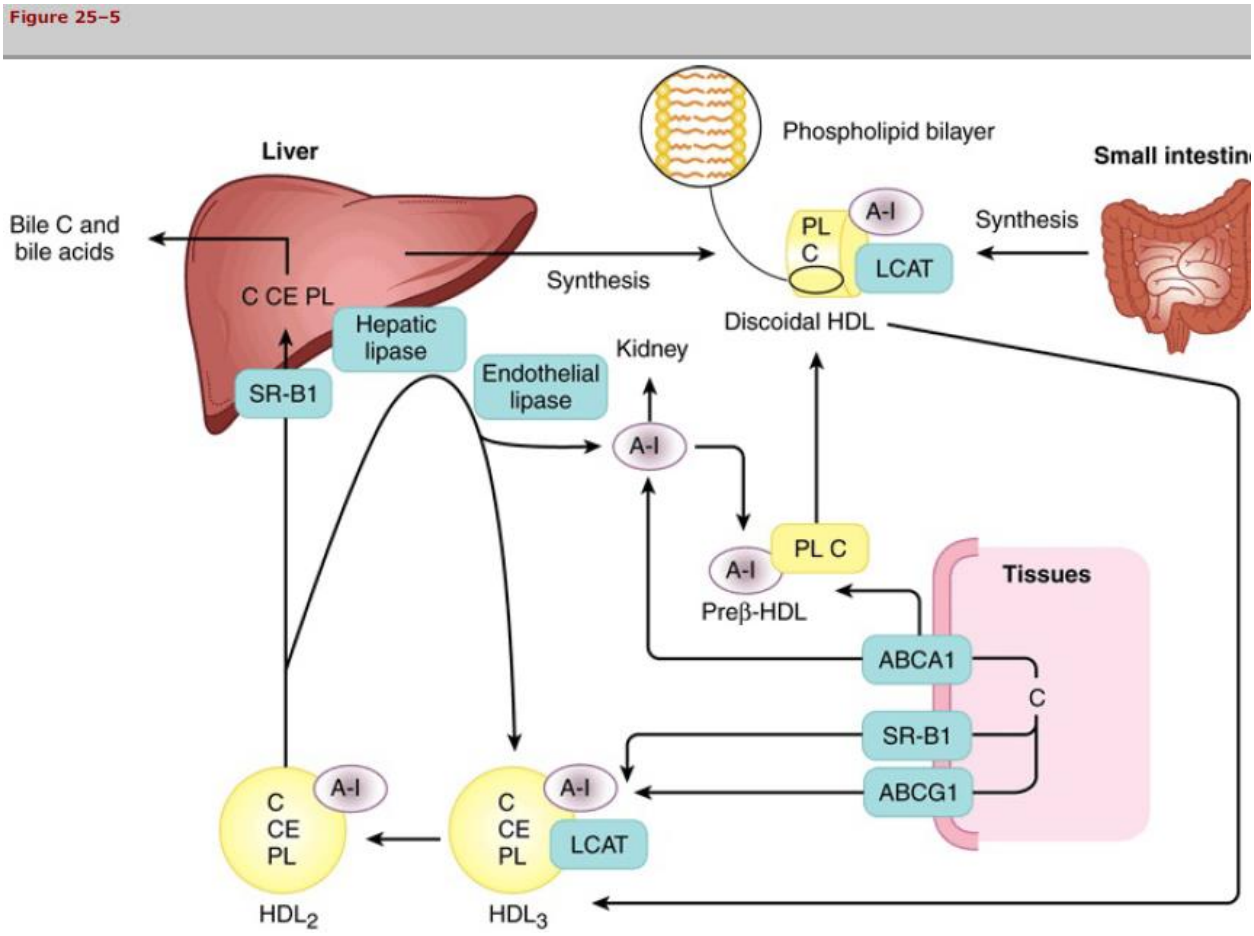
also takes up lipoproteins rich in apo E. Approximately 30% of LDL is degraded in extrahepatic tissues and 70% in the liver. A positive correlation exists between the incidence of **atherosclerosis** and the plasma concentration of LDL cholesterol. The LDL (apoB-100, E) receptor is defective in **familial hypercholesterolemia,** a genetic condition which blood LDL cholesterol levels are increased, causing premature atherosclerosis .

Lipid Transport & Storage

HDL TAKES PART IN BOTH LIPOPROTEIN TRIACYLGLYCEROL & CHOLESTEROL METABOLISM

HDL is synthesized and secreted from both liver and intestine (Figure 25–5). However, apo C and apo E are synthesized in the liver and transferred from liver HDL to intestinal HDL when the latter enters the plasma. A major function of HDL is to act as a repository for the apo C and apo E required in the metabolism of chylomicrons and VLDL. Nascent HDL consists of discoid phospholipid bilayers containing apo A and free cholesterol. These lipoproteins are similar to the particles found in the plasma of patients with a deficiency of the plasma enzyme **lecithin:cholesterol acyltransferase (LCAT)** and in the plasma of patients with **obstructive jaundice.** LCAT—and the LCAT activator apo A-I—bind to the discoidal particles, and the surface phospholipid and free cholesterol are converted into cholesteryl esters and lysolecithin (Chapter 24). The nonpolar cholesteryl esters move into the hydrophobic interior of the bilayer, whereas lysolecithin is transferred to plasma albumin. Thus, a nonpolar core is generated, forming a spherical, pseudomicellar HDL covered by a surface film of polar lipids and apolipoproteins. This aids the removal of excess unesterified cholesterol from lipoproteins and tissues as described below. The **class B scavenger receptor B1 (SR-B1)** has been identified as an **HDL receptor with a dual role in HDL metabolism.** In the liver and in steroidogenic tissues, it binds HDL via apo A-I, and cholesteryl ester is selectively delivered to the cells, although the particle itself, including apo A-I, is not taken up. In the tissues, on the other hand, SR-B1 mediates the acceptance of cholesterol effluxed from the cells by HDL, which then transports it to the liver for excretion via the bile (either as cholesterol or after conversion to bile acids) in the process known as **reverse cholesterol transport** (Figure 25–5). HDL3, generated from discoidal HDL by the action of LCAT, accepts cholesterol from the tissues via the **SR-B1** and the cholesterol is then esterified by LCAT, increasing the size of the particles to form the less dense HDL2. HDL3 is then reformed, either after selective delivery of cholesteryl ester to the liver via the SR-B1 or by hydrolysis of HDL2 phospholipid and triacylglycerol by hepatic lipase and endothelial lipase. This interchange of HDL2 and HDL3 is called the **HDL cycle** (Figure 25–5). Free apo A-I is released by these processes and forms **pre β-HDL** after associating with a minimum amount of phospholipid and cholesterol. Surplus apo A-I is destroyed in the kidney. A second important mechanism for

reverse cholesterol transport involves the **ATP-binding cassette transporters A1 (ABCA1) and G1 (ABCG1).** These transporters are members of a family of transporter proteins that couple the hydrolysis of ATP to the binding of a substrate, enabling it to be transported across the membrane. ABCG1 mediates the transport of cholesterol from cells to HDL, while ABCA1 preferentially promotes efflux to poorly lipidated particles such as pre β-HDL or apo A-1, which are then converted to HDL3 via discoidal HDL (Figure 25–5). Pre β-HDL is the most potent form of HDL inducing cholesterol efflux from the tissues.



HDL concentrations vary reciprocally with plasma triacylglycerol concentrations and directly with the activity of lipoprotein lipase. This may be due to surplus surface constituents, eg, phospholipid and apo A-I, being released during hydrolysis of chylomicrons and VLDL and contributing toward the formation of pre β-HDL and discoidal HDL. HDL2 concentrations are **inversely related to the incidence of atherosclerosis,** possibly because they reflect the efficiency of reverse cholesterol transport.

THE LIVER PLAYS A CENTRAL ROLE IN LIPID TRANSPORT & METABOLISM

The liver carries out the following major functions in lipid metabolism:
1. It facilitates the digestion and absorption of lipids by the production of **bile,** which contains cholesterol and bile salts synthesized within the liver de novo or after uptake of lipoprotein cholesterol.
2. It actively **synthesizes and oxidizes fatty acids** and also synthesizes triacylglycerols and phospholipids.
3. It **converts fatty acids to ketone bodies (ketogenesis)**.
4. It plays an integral part in the **synthesis and metabolism of plasma lipoproteins**.

Hepatic VLDL Secretion Is Related to Dietary & Hormonal Status

The cellular events involved in VLDL formation and secretion have been described above (Figure 25–2) and are shown in Figure 25–6. Hepatic triacylglycerol synthesis provides the immediate stimulus for the formation and secretion of VLDL. The fatty acids used are derived from two possible sources: (1) synthesis within the liver from **acetyl-CoA** derived mainly from carbohydrate (perhaps not so important in humans) and (2) uptake of **FFA** from the circulation. The first source is predominant in the well-fed condition, when fatty acid synthesis is high and the level of circulating FFA is low. As triacylglycerol does not normally accumulate in the liver in these conditions, it must be inferred that it is transported from the liver in VLDL as rapidly as it is synthesized. FFA from the circulation are the main source during starvation, the feeding of high-fat diets, or in diabetes mellitus, when hepatic lipogenesis is inhibited. Synthesis of VLDL takes place in the endoplasmic reticulum (ER) and requires the **microsomal triacylglycerol transfer proten (MTP),** which transfers triacylglycerol from the cytosol into the ER lumen where it is incorporated into particles with cholesterol, phospholipids and apoB-100 (Figure 25–6). Factors that enhance both the synthesis of triacylglycerol and the secretion of VLDL by the liver include (1) the fed state rather than the starved state; (2) the feeding of diets high in carbohydrate (particularly if they contain sucrose or fructose), leading to high rates of lipogenesis and esterification of fatty acids; (3) high levels of circulating FFA; (4) ingestion of ethanol; and (5) the presence of high

concentrations of insulin and low concentrations of glucagon, which enhance fatty acid synthesis and esterification and inhibit their oxidation (Figure 25–6).

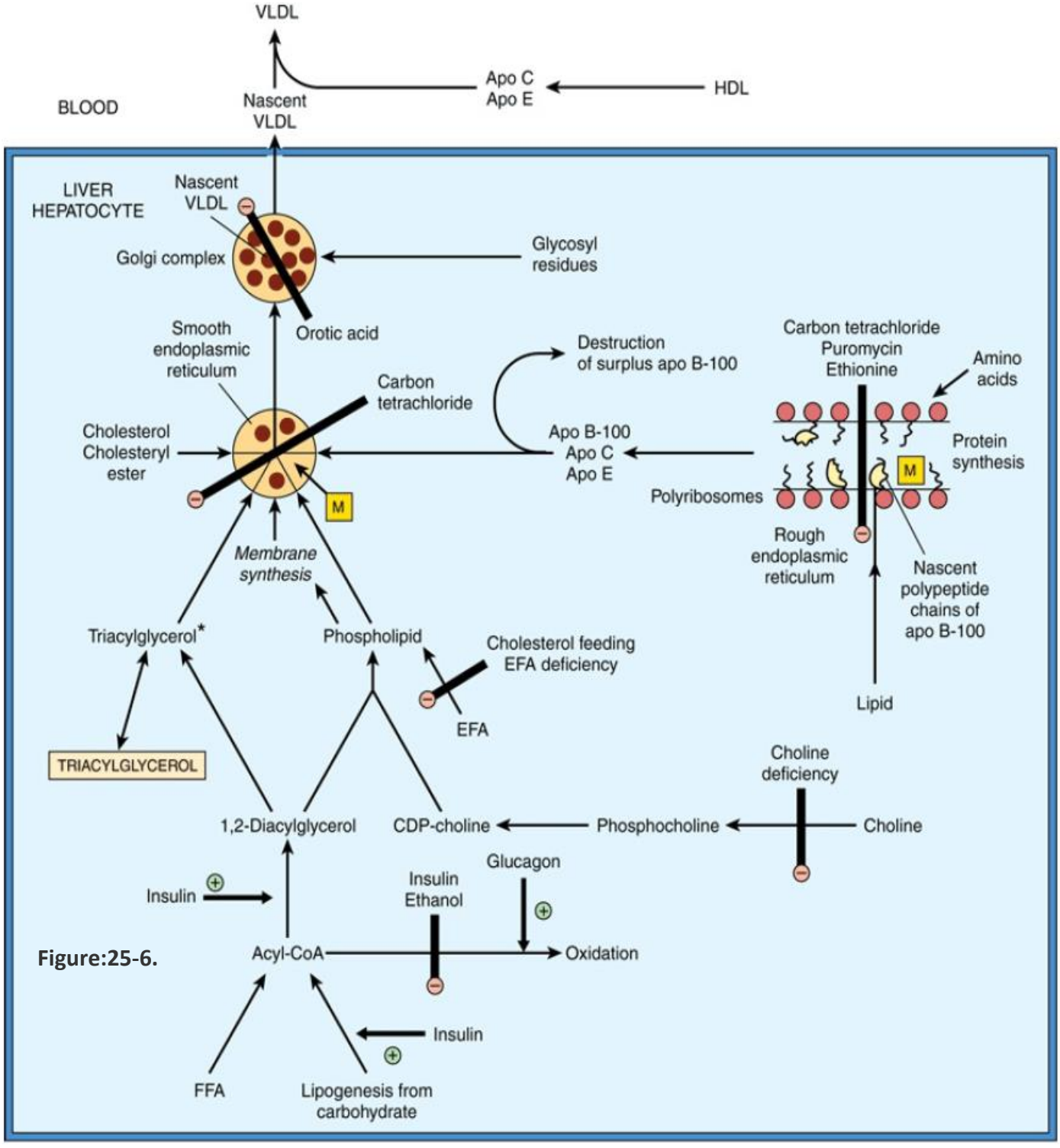
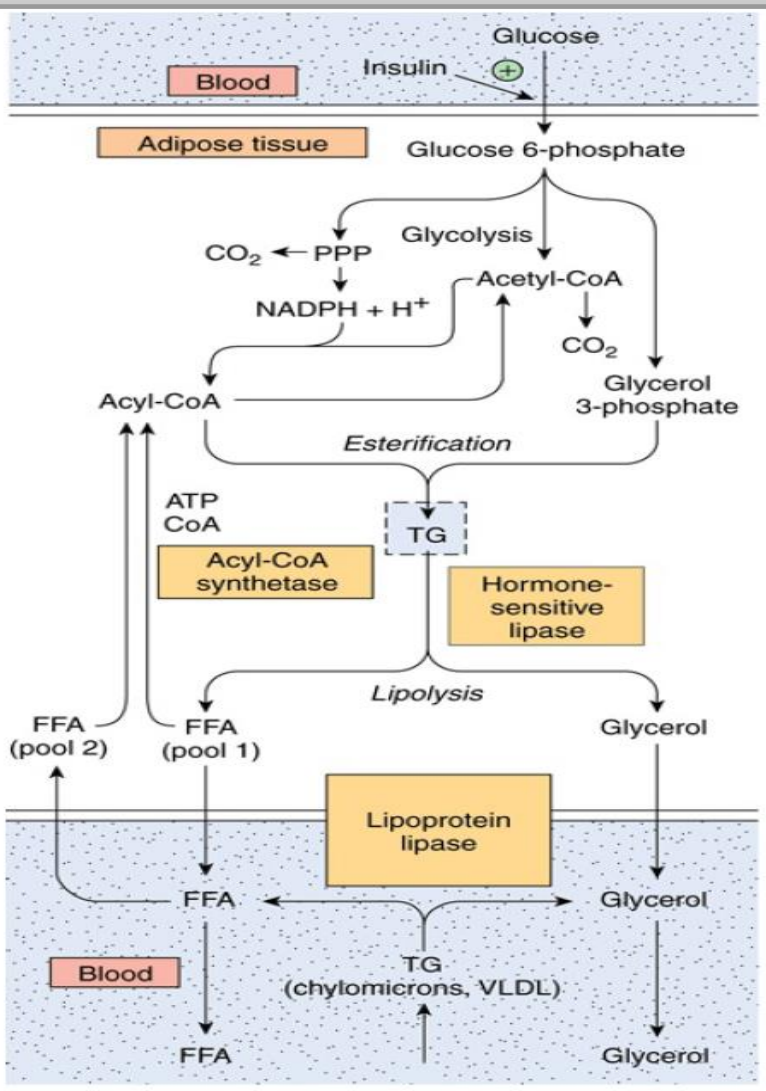


Figure:25-6.

ADIPOSE TISSUE IS THE MAIN STORE OF TRIACYLGLYCEROL IN THE BODY

Triacylglycerols are stored in adipose tissue in large **lipid droplets** and are continually undergoing lipolysis (hydrolysis) and re-esterification (Figure 25–7). These two processes are entirely different pathways involving different reactants and enzymes. This allows the processes of esterification or lipolysis to be regulated separately by many nutritional, metabolic, and hormonal factors. The balance between these two processes determines the magnitude of the FFA pool in adipose tissue, which in turn determines the level of FFA circulating in the plasma. Since the latter has most profound effects upon the metabolism of other tissues, particularly liver and muscle, the factors operating in adipose tissue that regulate the outflow of FFA exert an influence far beyond the tissue itself.

Figure 25–7



The Provision of Glycerol 3-Phosphate Regulates Esterification: Lipolysis Is Controlled by Hormone-Sensitive Lipase

Triacylglycerol is synthesized from acyl-CoA and glycerol 3-phosphate. Since the enzyme **glycerol kinase** is not expressed in adipose tissue, glycerol cannot be utilized for the provision of glycerol 3-phosphate, which must be supplied from glucose via glycolysis.

Triacylglycerol undergoes hydrolysis by a **hormone-sensitive lipase** to form FFA and glycerol. This lipase is distinct from lipoprotein lipase, which catalyzes lipoprotein triacylglycerol hydrolysis before its uptake into extrahepatic tissues (see above). Since the glycerol cannot be utilized, it enters the blood and is taken up and transported to tissues such as the liver and kidney, which possess an active glycerol kinase. The FFA formed by lipolysis can be reconverted in adipose tissue to acyl-CoA by **acyl-CoA synthetase** and reesterified with glycerol 3-phosphate to form triacylglycerol. Thus, **there is a continuous cycle of lipolysis and re-esterification within the tissue.** However, when the rate of re-esterification is not sufficient to match the rate of lipolysis, FFA accumulate and diffuse into the plasma, where they bind to albumin and raise the concentration of plasma-free fatty acids.

Increased Glucose Metabolism Reduces the Output of FFA

When the utilization of glucose by adipose tissue is increased, the FFA outflow decreases. However, the release of glycerol continues, demonstrating that the effect of glucose is not mediated by reducing the rate of lipolysis. The effect is due to the provision of glycerol 3-phosphate, which enhances esterification of FFA. Glucose can take several pathways in adipose tissue, including oxidation to CO2 via the citric acid cycle, oxidation in the pentose phosphate pathway, conversion to long-chain fatty acids, and formation of acylglycerol via glycerol 3-phosphate (Figure 25–7). When glucose utilization is high, a larger proportion of the uptake is oxidized to CO2 and converted to fatty acids. However, as total glucose utilization decreases, the greater proportion of the glucose is directed to the formation of glycerol 3-phosphate for the esterification of acylCoA, which helps to minimize the efflux of FFA.

HORMONES REGULATE FAT MOBILIZATION

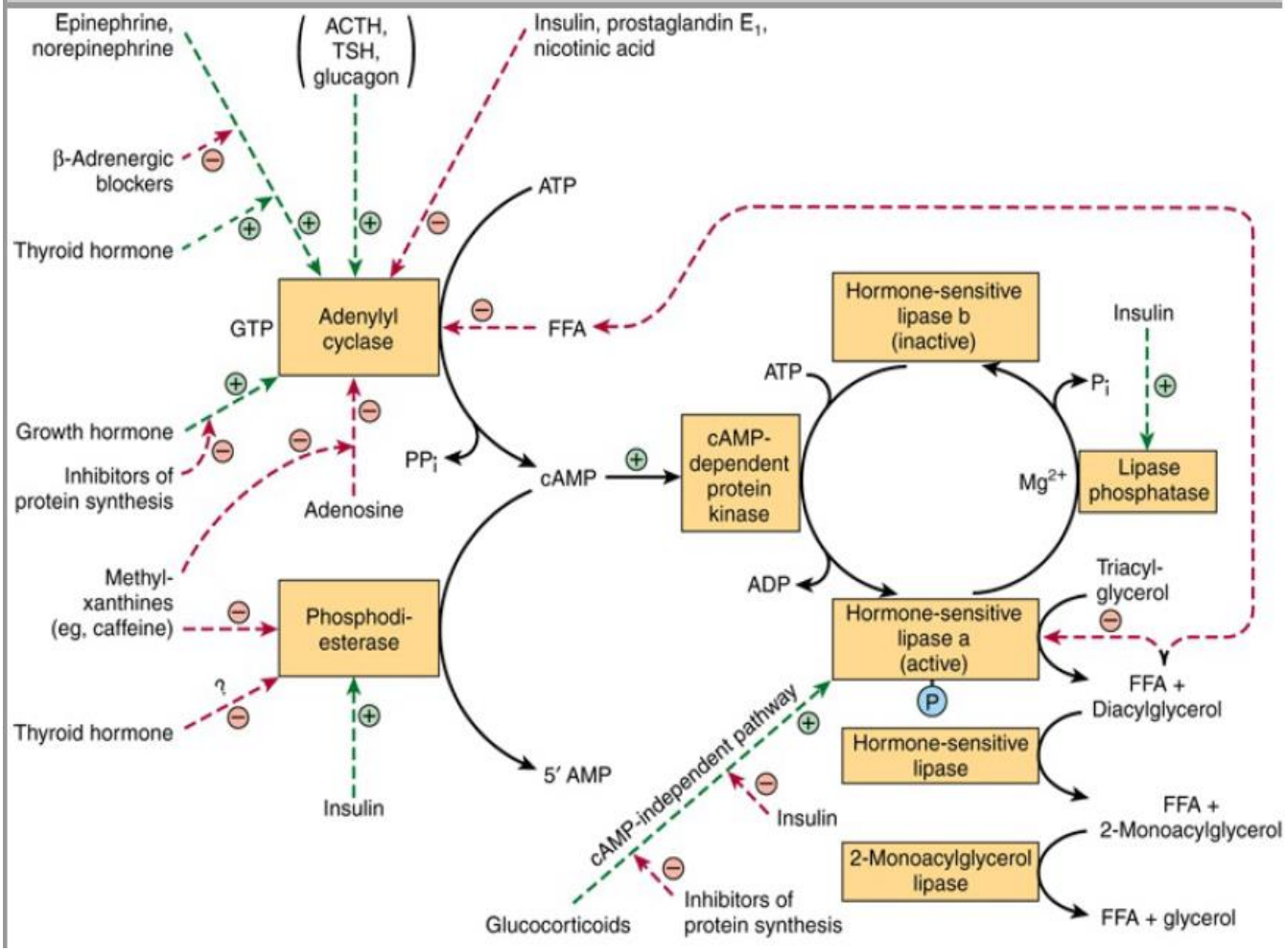
Adipose Tissue Lipolysis Is Inhibited by Insulin

The rate of release of FFA from adipose tissue is affected by many hormones that influence either the rate of esterification or the rate of lipolysis. **Insulin** inhibits the release of FFA from adipose tissue, which is followed by a fall in circulating plasma free fatty acids. Insulin also enhances lipogenesis and the synthesis of acylglycerol and increases the oxidation of glucose to CO2 via the pentose phosphate pathway. All of these effects are dependent on the presence of glucose and can be explained, to a large extent, on the basis of the ability of insulin to enhance the uptake of glucose into adipose cells via the **GLUT 4 transporter.** In addition, insulin increases the activity of the enzymes pyruvate dehydrogenase, acetyl-CoA carboxylase, and glycerol phosphate acyltransferase, reinforcing the effects of increased glucose uptake on the enhancement of fatty acid and acylglycerol synthesis. These three enzymes are regulated in a coordinate manner by phosphorylation–dephosphorylation mechanisms.
Another principal action of insulin in adipose tissue is to inhibit the activity of **hormone-sensitive lipase,** reducing the release not only of FFA but also of glycerol. Adipose tissue is much more sensitive to insulin than many other tissues, which points to adipose tissue as a major site of insulin action in vivo.

Several Hormones Promote Lipolysis

Other hormones accelerate the release of FFA from adipose tissue and raise the plasma-free fatty acid concentration by increasing the rate of lipolysis of the triacylglycerol stores (Figure 25–8). These include **epinephrine, norepinephrine, glucagon, adrenocorticotropic hormone (ACTH), α- and β-melanocyte-stimulating hormones (MSH), thyroidstimulating hormone (TSH), growth hormone (GH), and vasopressin.** Many of these activate hormone-sensitive lipase. For an optimal effect, most of these lipolytic processes require the presence of **glucocorticoids** and **thyroid hormones.** These hormones act in a **facilitatory** or **permissive** capacity with respect to other lipolytic endocrine factors.

Figure 25–8



The hormones that act rapidly in promoting lipolysis, ie, catecholamines (epinephrine and nor-epinephrine), do so by stimulating the activity of **adenylyl cyclase,** the enzyme that converts ATP to cAMP. The mechanism is analogous to that responsible for hormonal stimulation of glycogenolysis (Chapter 19). cAMP, by stimulating **cAMP-dependent protein kinase,** activates hormone-sensitive lipase. Thus, processes which destroy or preserve cAMP influence lipolysis. cAMP is degraded to 5'-AMP by the enzyme **cyclic 3',5'-nucleotide phosphodiesterase.** This enzyme is inhibited by methylxanthines such as **caffeine** and **theophylline. Insulin** antagonizes the effect of the lipolytic hormones. Lipolysis appears to be more sensitive to changes in concentration of insulin than are glucose utilization and esterification. The antilipolytic effects of insulin, nicotinic acid, and

prostaglandin E1 are accounted for by inhibition of the synthesis of cAMP at the adenylyl cyclase site, acting through a Gi protein. Insulin also stimulates phosphodiesterase and the lipase phosphatase that inactivates hormone-sensitive lipase. The effect of growth hormone in promoting lipolysis is dependent on synthesis of proteins involved in the formation of cAMP. Glucocorticoids promote lipolysis via synthesis of new lipase protein by a cAMP-independent pathway, which may be inhibited by insulin, and also by promoting transcription of genes involved in the cAMP signal cascade.

Perilipin Regulates the Balance between Triacylglycerol Storage and Lipolysis in Adipocytes

Perilipin, a protein involved in the formation of lipid droplets in adipocytes, inhibits lipolysis in basal conditions by preventing access of the lipase enzymes to the stored triacylglycerols. On stimulation with hormones which promote triacylglycerol degradation, however, the protein targets hormone-sensitive lipase to the lipid droplet surface and thus promotes lipolysis. Perilipin, therefore, enables the storage and breakdown of triacylglycerol to be coordinated according to the metabolic needs of the body.

Human Adipose Tissue May Not Be an Important Site of Lipogenesis

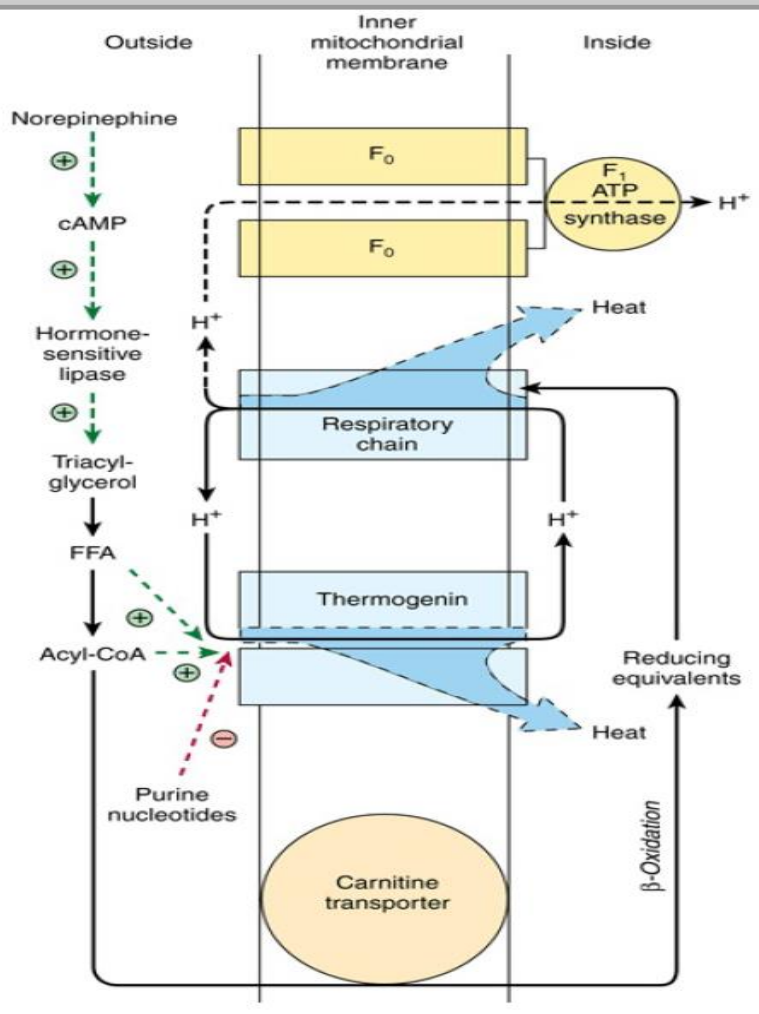
In adipose tissue, there is no significant incorporation of glucose or pyruvate into long-chain fatty acids, ATP-citrate lyase, a key enzyme in lipogenesis, does not appear to be present, and other lipogenic enzymes—eg, glucose-6-phosphate dehydrogenase and the malic enzyme—do not undergo adaptive changes. Indeed, it has been suggested that in humans there is a**"carbohydrate excess syndrome"** due to a unique limitation in ability to dispose of excess carbohydrate by lipogenesis. In birds, lipogenesis is confined to the liver, where it is particularly important in providing lipids for egg formation, stimulated by estrogens.

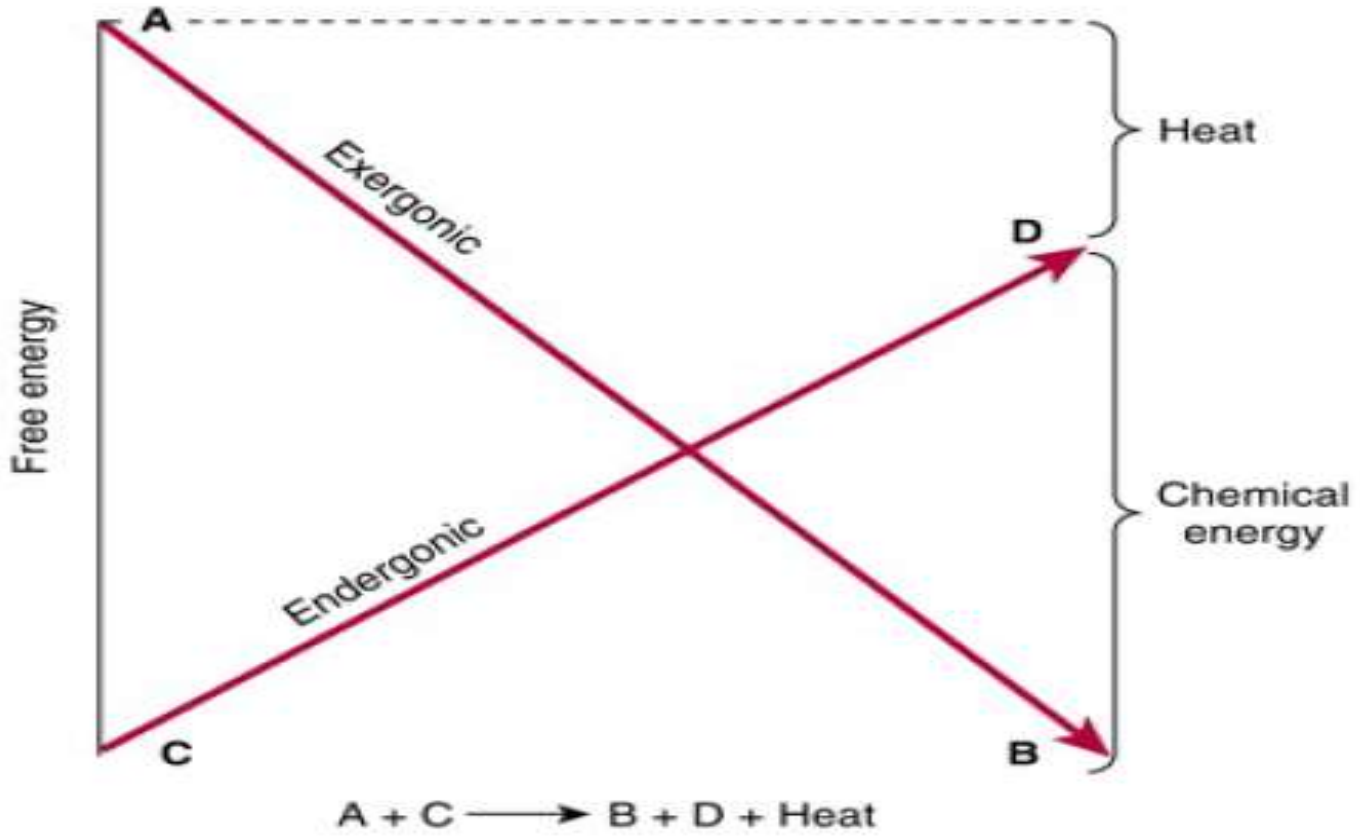
BROWN ADIPOSE TISSUE PROMOTES THERMOGENESIS

Brown adipose tissue is involved in metabolism, particularly at times when heat generation is necessary. Thus, the tissue is extremely active in some species, for example, during arousal from hibernation, in animals exposed to cold

(nonshivering thermogenesis), and in heat production in the newborn. Though not a prominent tissue in humans, it is present in normal individuals, where it could be responsible for **"diet-induced thermogenesis."** It is noteworthy that brown adipose tissue is reduced or absent in obese persons. The tissue is characterized by a well-developed blood supply and a high content of mitochondria and cytochromes, but low activity of ATP synthase. Metabolic emphasis is placed on oxidation of both glucose and fatty acids. **Norepinephrine** liberated from sympathetic nerve endings is important in increasing lipolysis in the tissue and increasing synthesis of lipoprotein lipase to enhance utilization of triacylglycerol-rich lipoproteins from the circulation. Oxidation and phosphorylation are not coupled in mitochondria of this tissue, and the phosphorylation that does occur is at the substrate level, eg, at the succinate thiokinase step and in glycolysis. Thus, **oxidation produces much heat, and little free energy is trapped in ATP.** A thermogenic uncoupling protein, **thermogenin,** acts as a proton conductance pathway dissipating the electrochemical potential across the mitochondrial membrane (Figure 25–9).

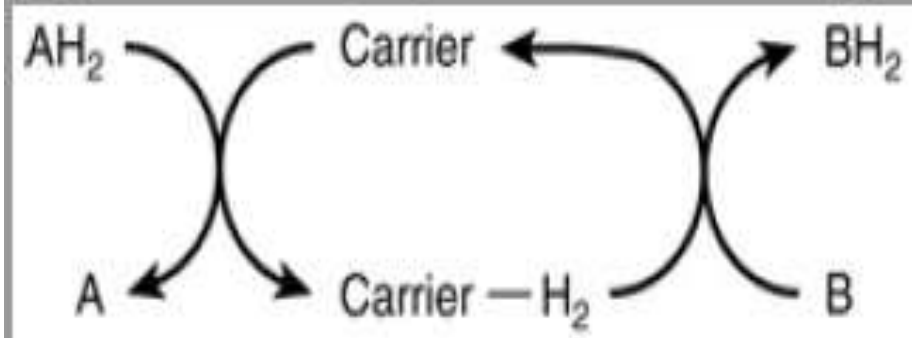
Figure 25–9

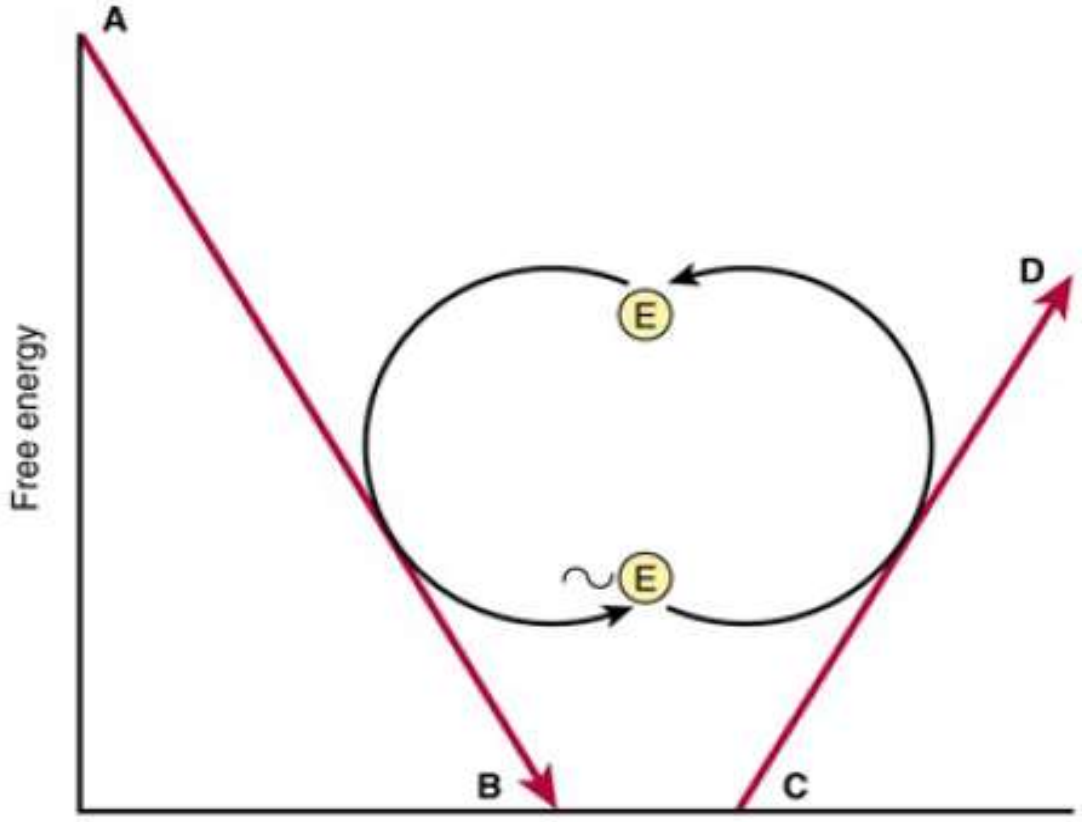



A
Exergonic
Heat
D
Free energy
Endergonic
Chemical energy
C
B
A + C ⟶ B + D + Heat

$$A + C \rightarrow I \rightarrow B + D$$

Figure 11–2




A
Free energy
E
D
E
B
C

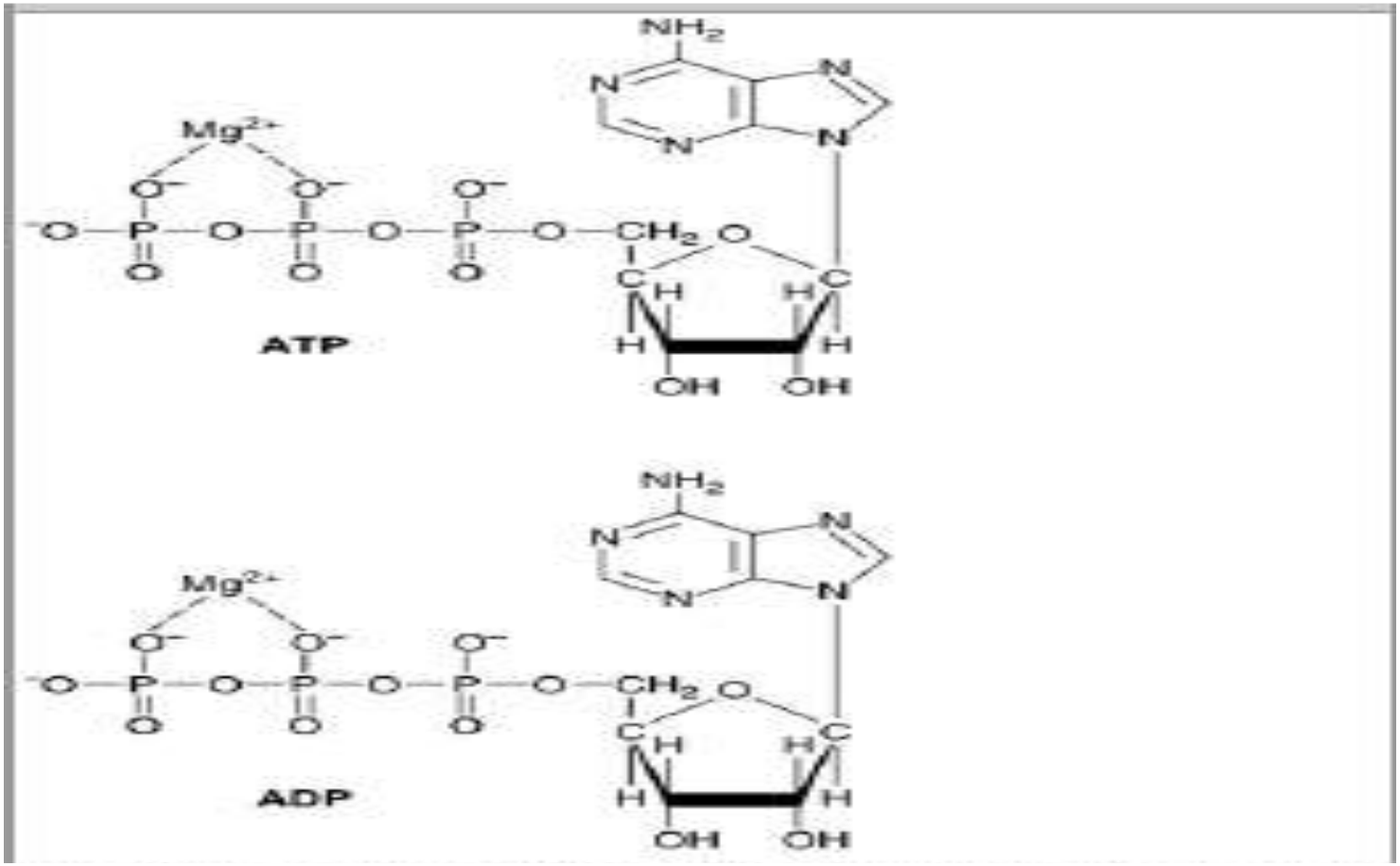
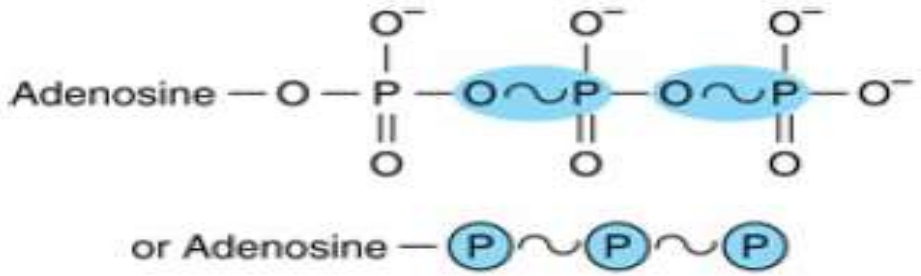
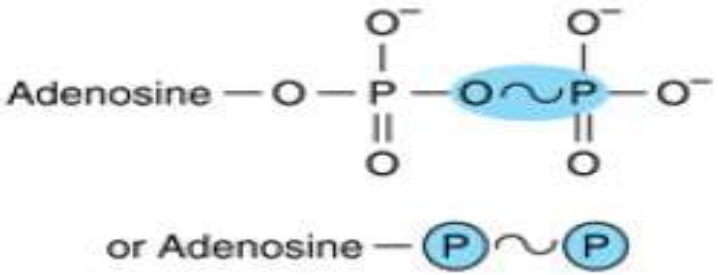

ATP
ADP

Table 11-1 Standard Free Energy of Hydrolysis of Some Organophosphates of Biochemical Importance

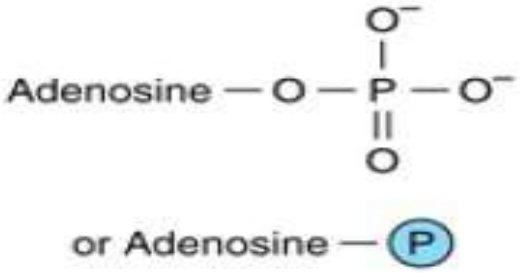
	$\Delta G^{0'}$	
Compound	**kJ/mol**	**kcal/mol**
Phosphoenolpyruvate	-61.9	-14.8
Carbamoyl phosphate	-51.4	-12.3
1,3-Bisphosphoglycerate (to 3-phosphoglycerate)	-49.3	-11.8
Creatine phosphate	-43.1	-10.3
ATP $\rightarrow$ AMP + PP_i	-32.2	-7.7
ATP $\rightarrow$ ADP + P_i	-30.5	-7.3
Glucose 1-phosphate	-20.9	-5.0
PP_i	-19.2	-4.6
Fructose 6-phosphate	-15.9	-3.8
Glucose 6-phosphate	-13.8	-3.3
Glycerol 3-phosphate	-9.2	-2.2



Adenosine triphosphate (ATP)



Adenosine diphosphate (ADP)



Adenosine monophosphate (AMP)

Figure 11–7

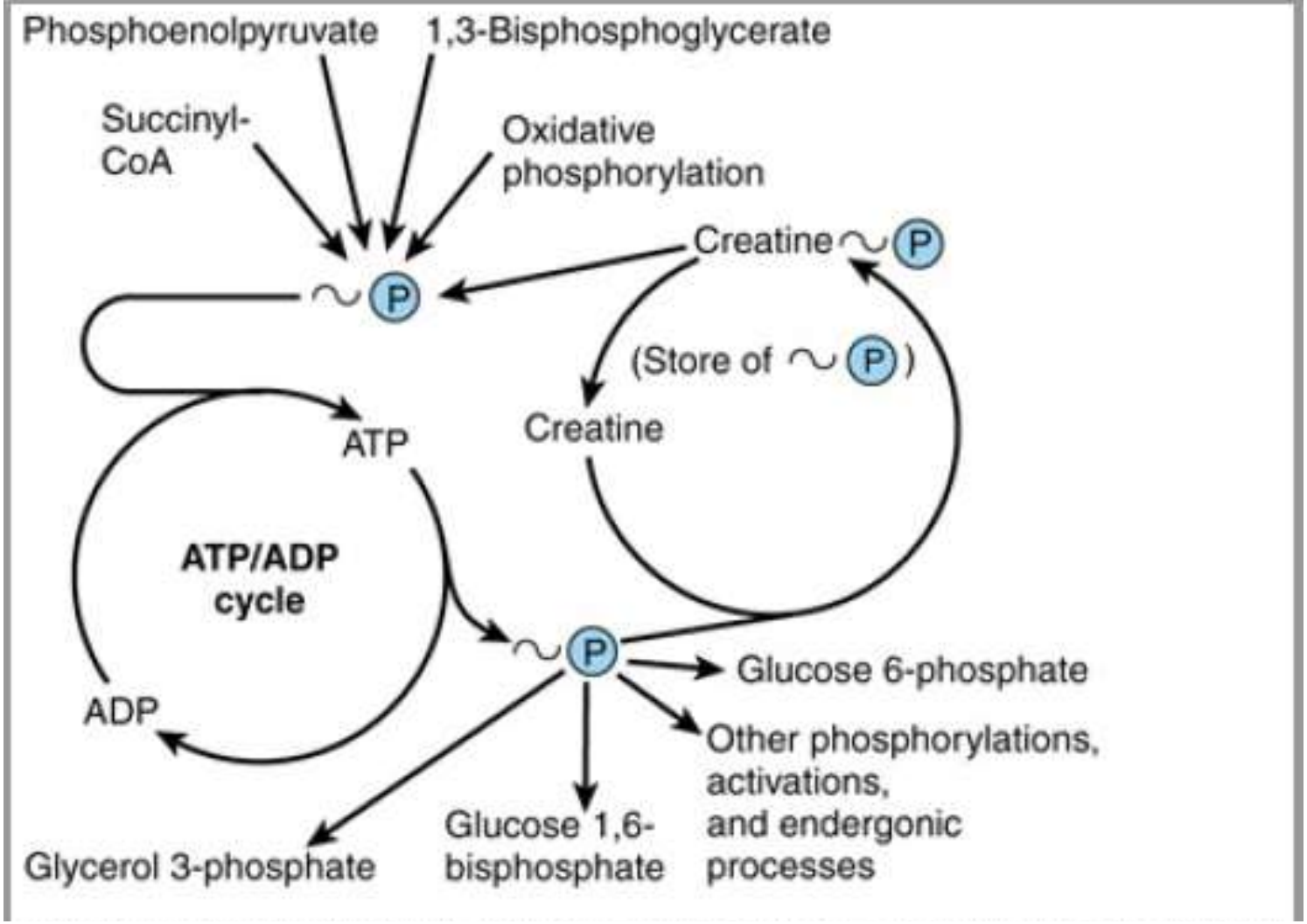
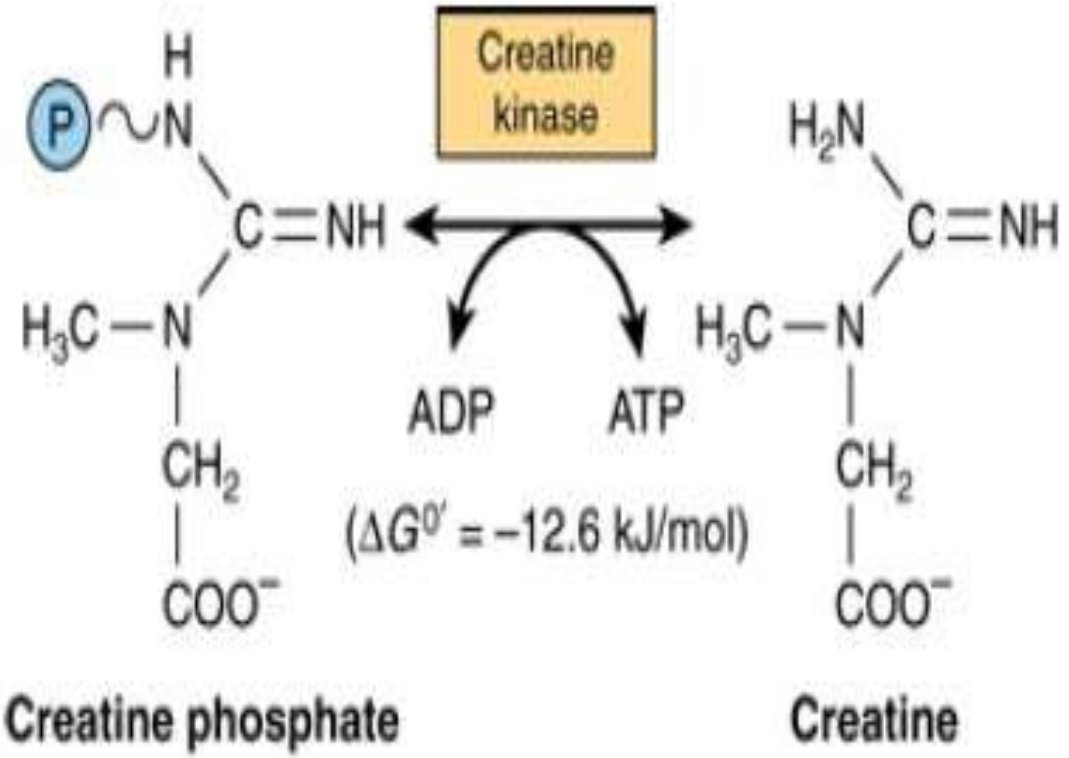

Phosphoenolpyruvate
1,3-Bisphosphoglycerate
Succinyl-CoA
Oxidative phosphorylation
Creatine ~ P
~ P
(Store of ~ P)
Creatine
ATP
ATP/ADP cycle
~ P
Glucose 6-phosphate
ADP
Other phosphorylations, activations, and endergonic processes
Glucose 1,6-bisphosphate
Glycerol 3-phosphate

Figure 11–8

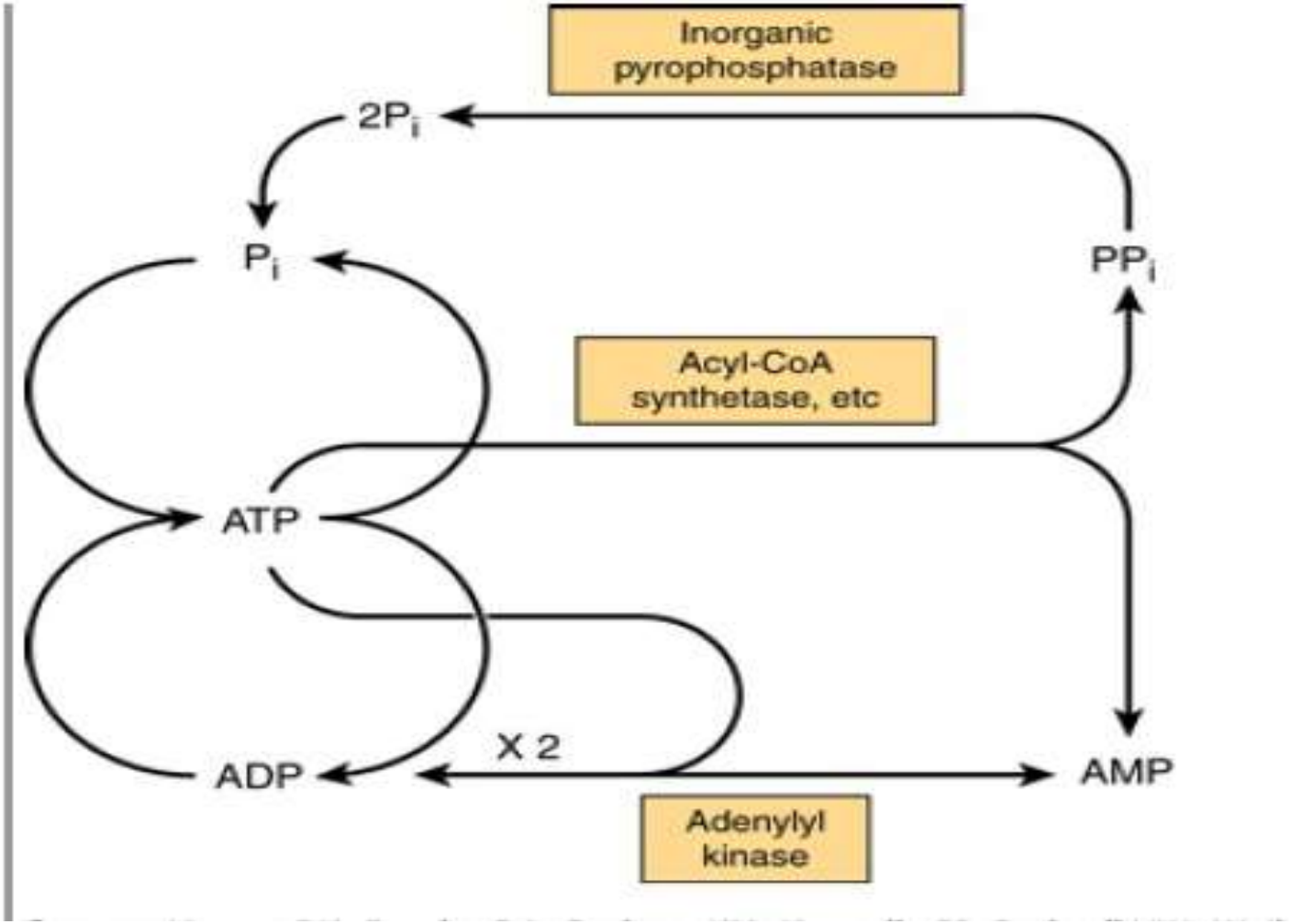

Creatine kinase
ADP
ATP
(ΔG°′ = –12.6 kJ/mol)
Creatine phosphate
Creatine

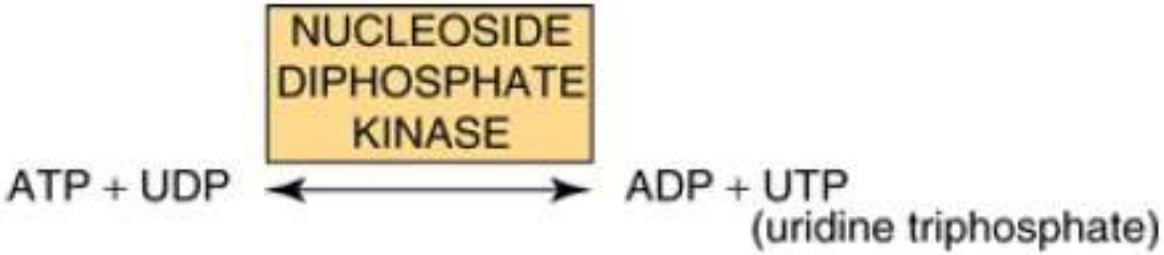
This allows:

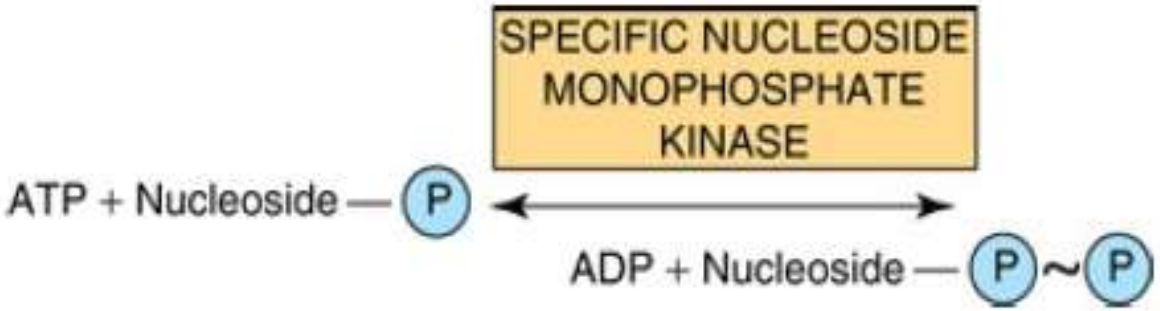
1. **High-energy phosphate in ADP to be used in the synthesis of ATP.**

2. AMP, formed as a consequence of several activating reactions involving ATP, to be recovered by rephosphorylation to ADP.

3. AMP to increase in concentration when ATP becomes depleted and act as a metabolic (allosteric) signal to increase the rate of catabolic reactions, which in turn lead to the generation of more ATP .


Inorganic pyrophosphatase
2Pi
Pi
PPi
Acyl-CoA synthetase, etc
ATP
X 2
ADP
AMP
Adenylyl kinase

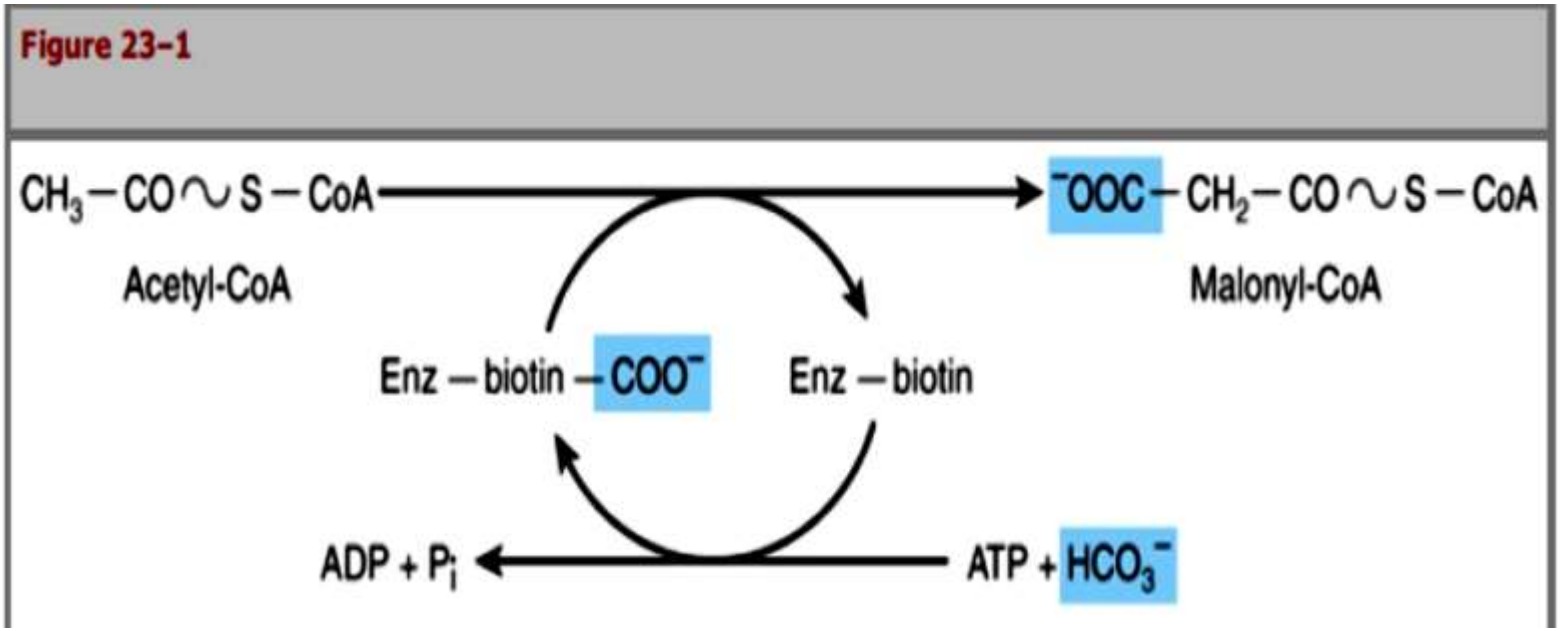

NUCLEOSIDE
DIPHOSPHATE
KINASE
ATP + UDP
ADP + UTP
(uridine triphosphate)


SPECIFIC NUCLEOSIDE
MONOPHOSPHATE
KINASE
ATP + Nucleoside — P
ADP + Nucleoside — P ~ P

BIOSYNTHESIS OF FATTY ACIDS

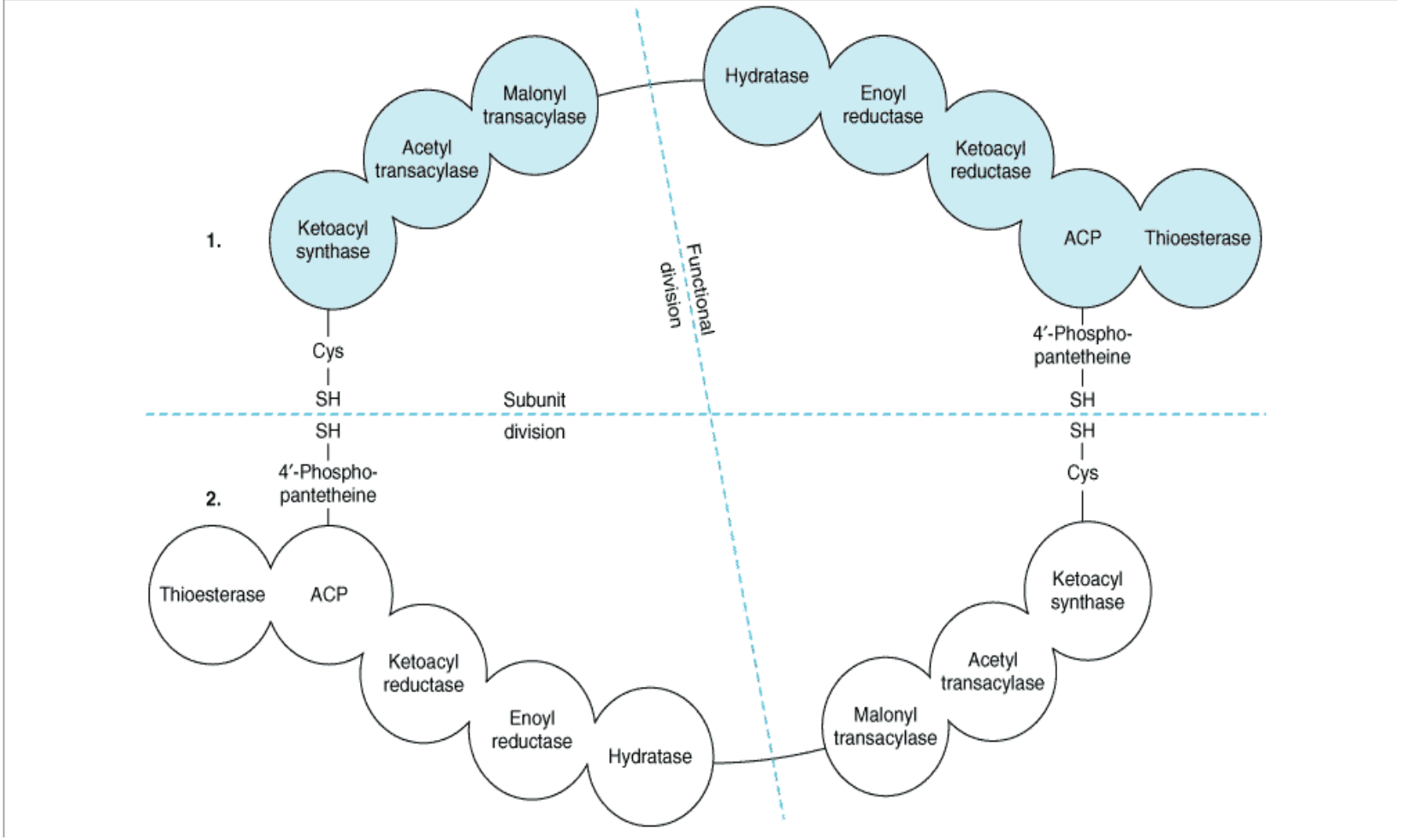
Lipogenesis.

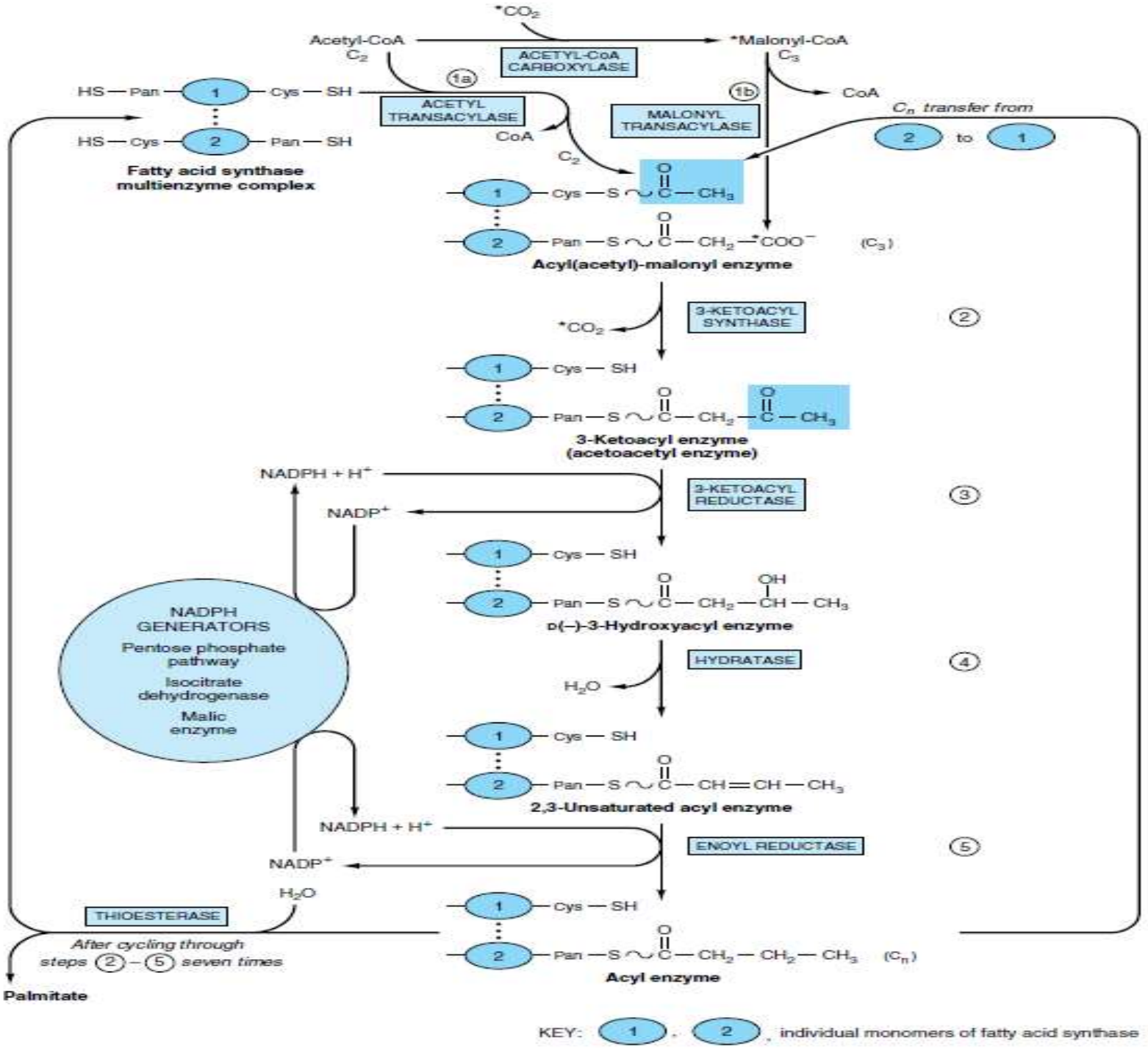
Production of Malonyl-CoA Is the Initial & Controlling Step in Fatty Acid Synthesis



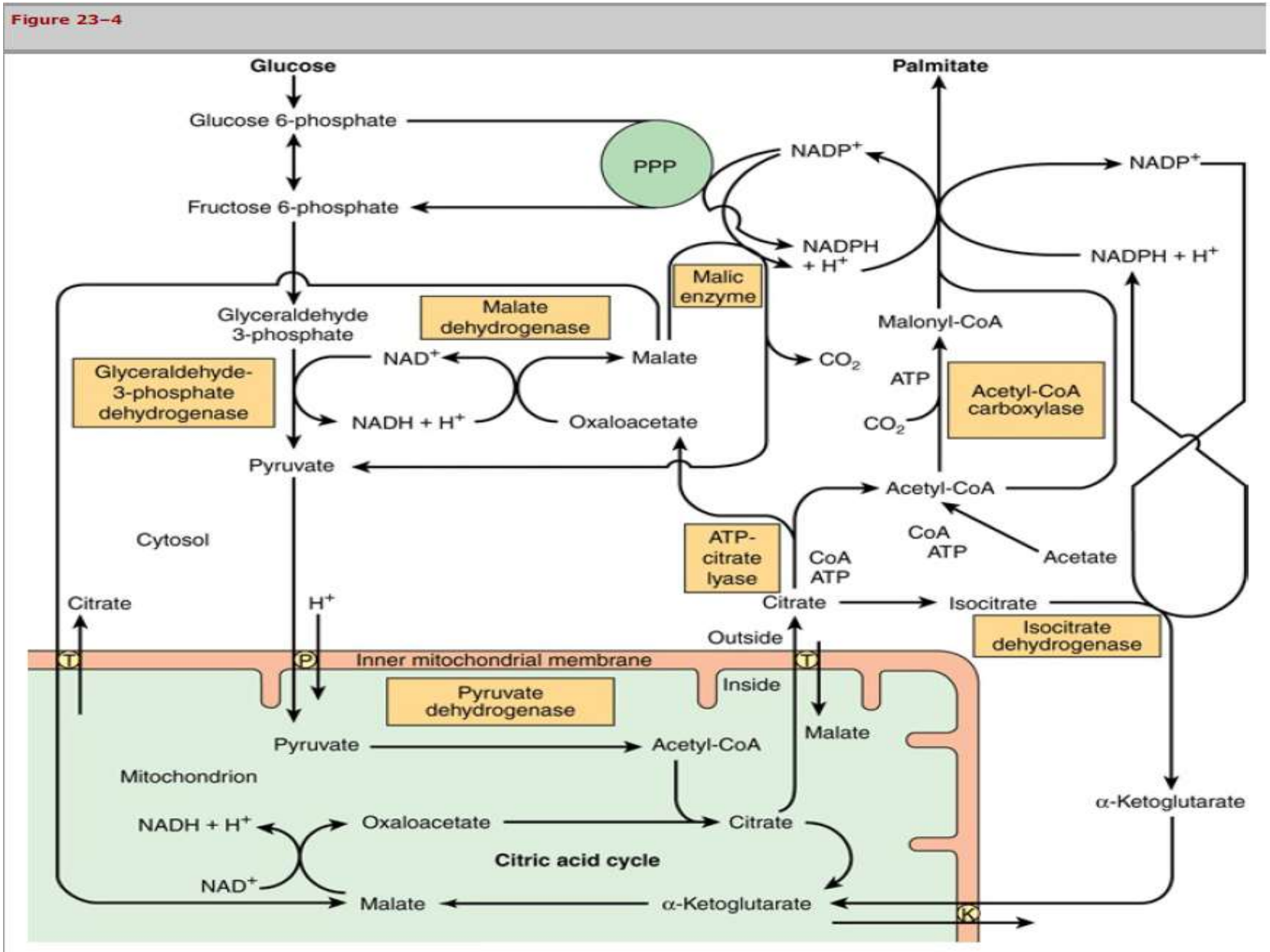
The Fatty Acid Synthase Complex Is a Polypeptide Containing Seven Enzyme Activities

Figure 23–2.



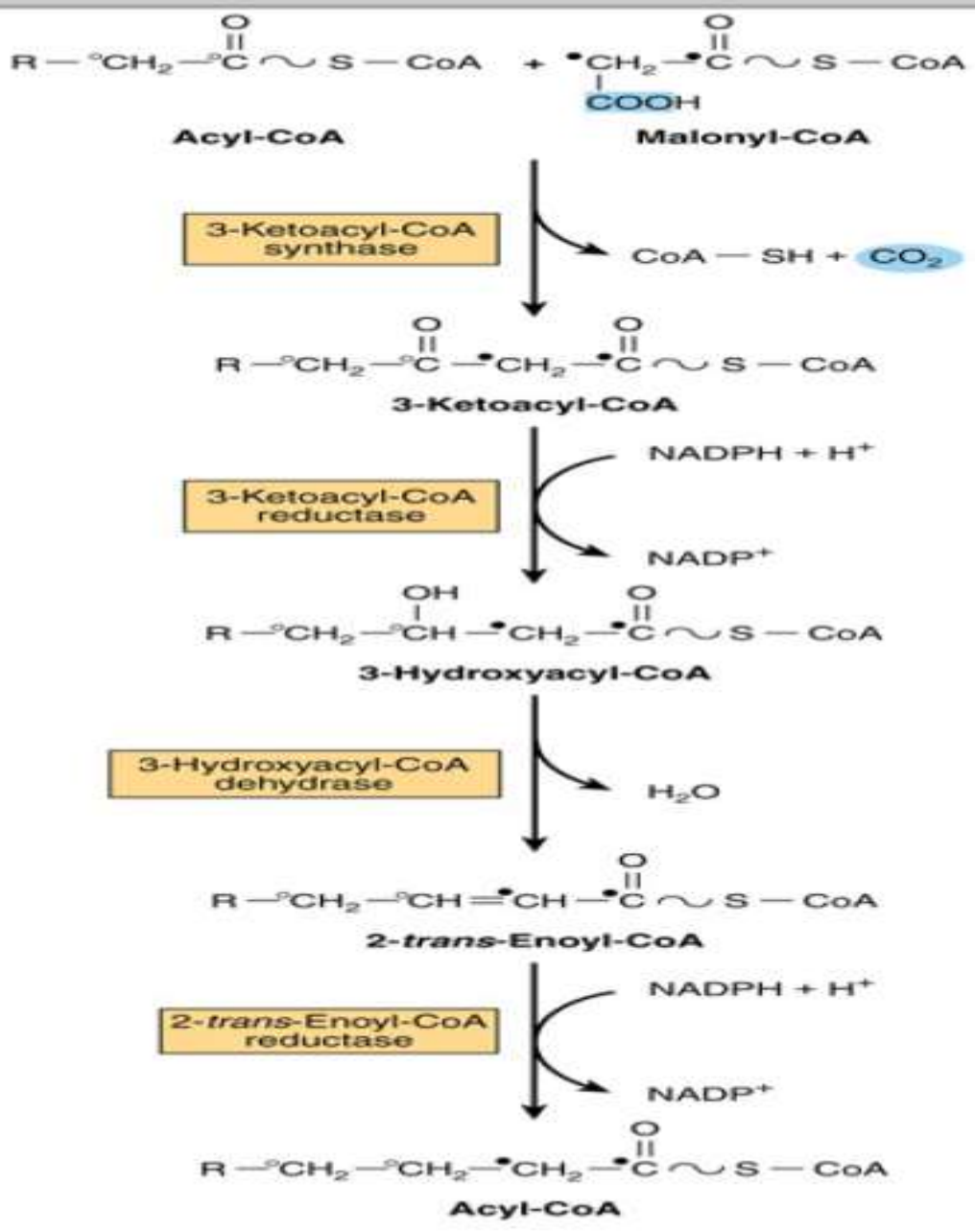

*CO2
Acetyl-CoA
C2
ACETYL-CoA CARBOXYLASE
*Malonyl-CoA
C3
CoA
1a
1b
ACETYL TRANSACYLASE
MALONYL TRANSACYLASE
HS — Pan — 1 — Cys — SH
HS — Cys — 2 — Pan — SH
Fatty acid synthase multienzyme complex
Cn transfer from 2 to 1
1 — Cys — S — C — CH3
2 — Pan — S — C — CH2 — *COO− (C3)
Acyl(acetyl)-malonyl enzyme
*CO2
3-KETOACYL SYNTHASE
2
1 — Cys — SH
2 — Pan — S — C — CH2 — C — CH3
3-Ketoacyl enzyme (acetoacetyl enzyme)
NADPH + H+
NADP+
3-KETOACYL REDUCTASE
3
1 — Cys — SH
2 — Pan — S — C — CH2 — CH — CH3 (OH)
D(−)-3-Hydroxyacyl enzyme
NADPH GENERATORS
Pentose phosphate pathway
Isocitrate dehydrogenase
Malic enzyme
HYDRATASE
4
H2O
1 — Cys — SH
2 — Pan — S — C — CH=CH — CH3
2,3-Unsaturated acyl enzyme
NADPH + H+
NADP+
ENOYL REDUCTASE
5
H2O
THIOESTERASE
1 — Cys — SH
2 — Pan — S — C — CH2 — CH2 — CH3 (Cn)
Acyl enzyme
After cycling through steps 2 – 5 seven times
Palmitate
KEY: 1 , 2 , individual monomers of fatty acid synthase

- **The Main Source of NADPH for Lipogenesis Is the Pentose Phosphate Pathway**
- **Acetyl-CoA Is the Principal Building Block of Fatty Acids**

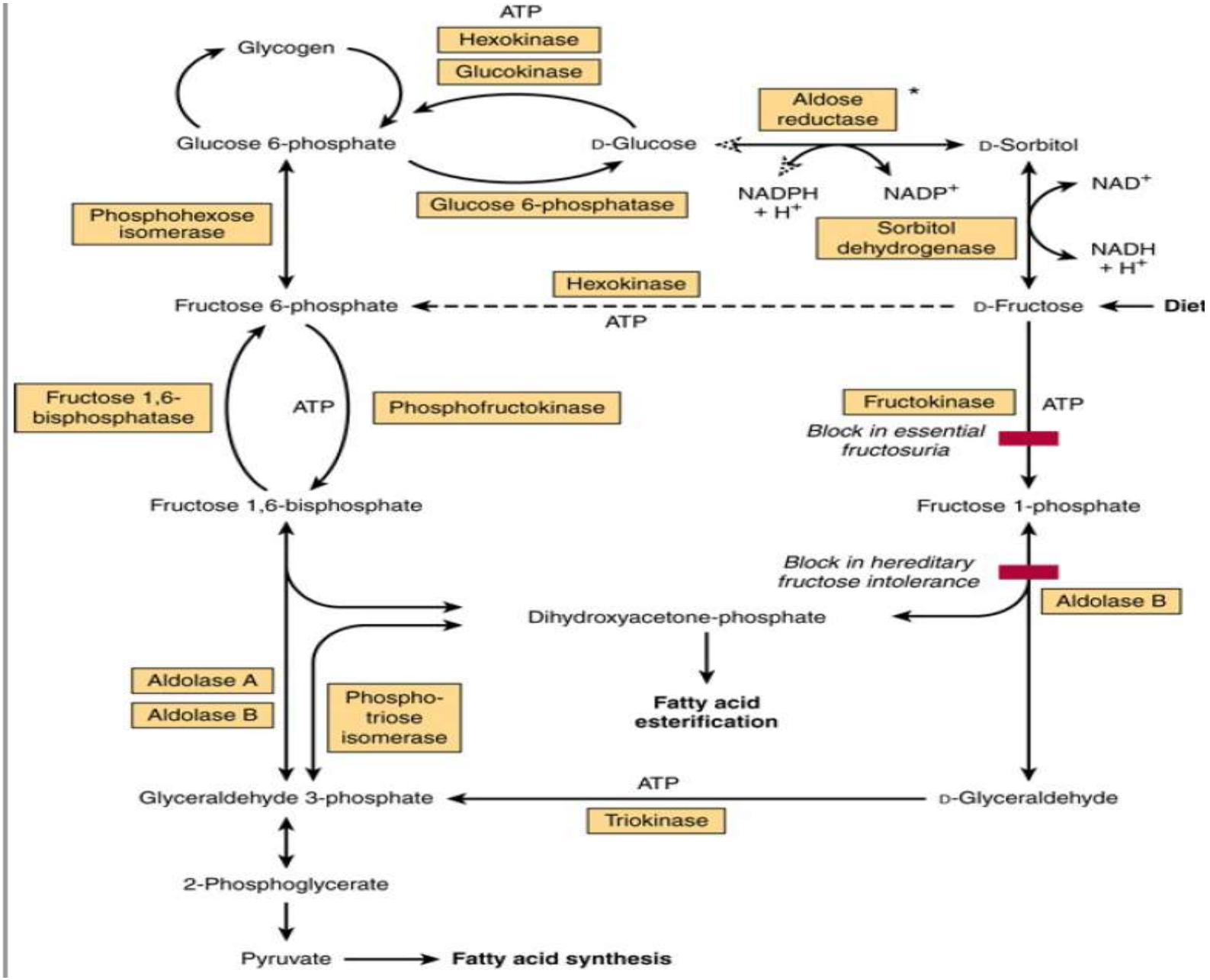


Elongation of Fatty Acid Chains Occurs in the Endoplasmic Reticulum

Figure 23–5

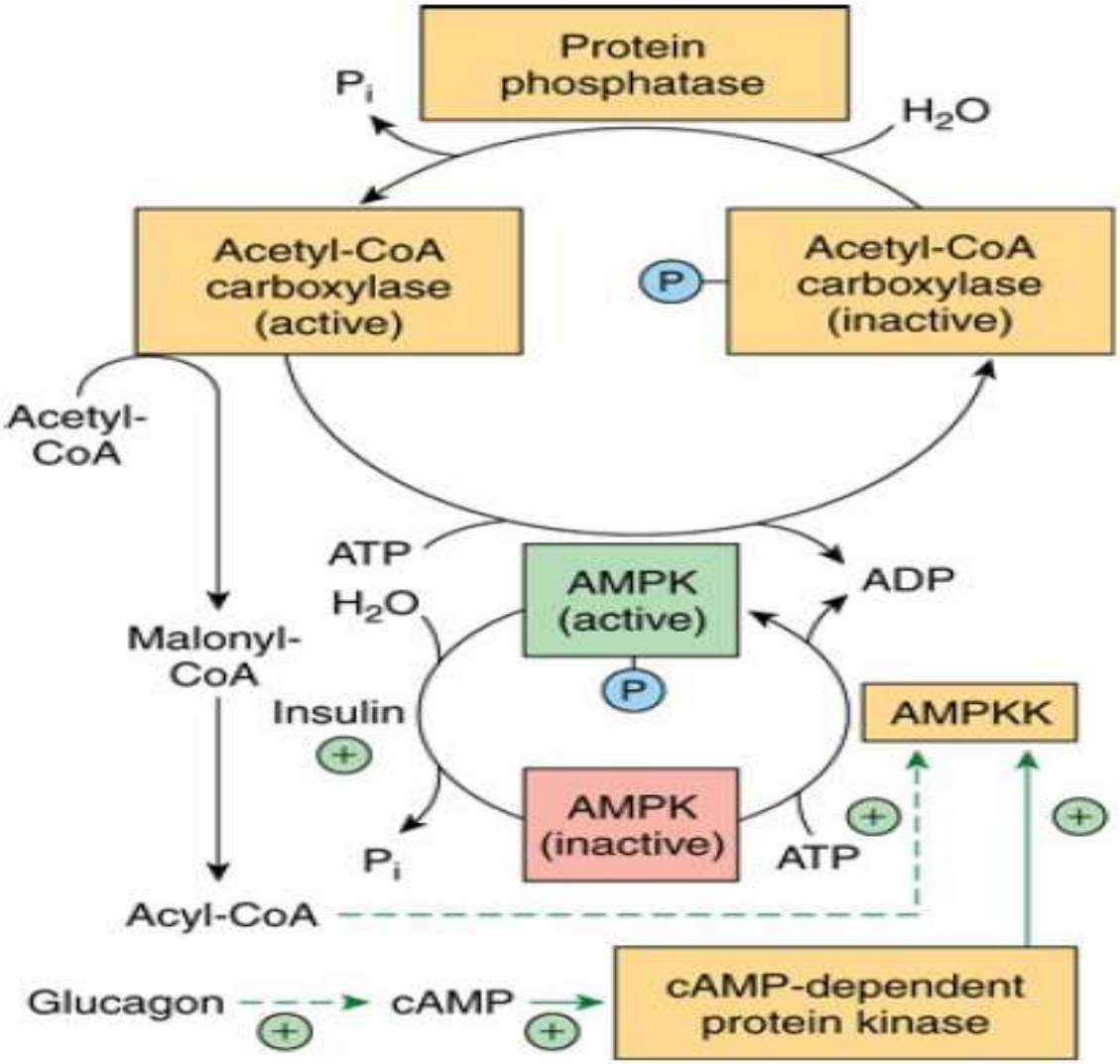


1. THE NUTRITIONAL STATE REGULATES LIPOGENESIS

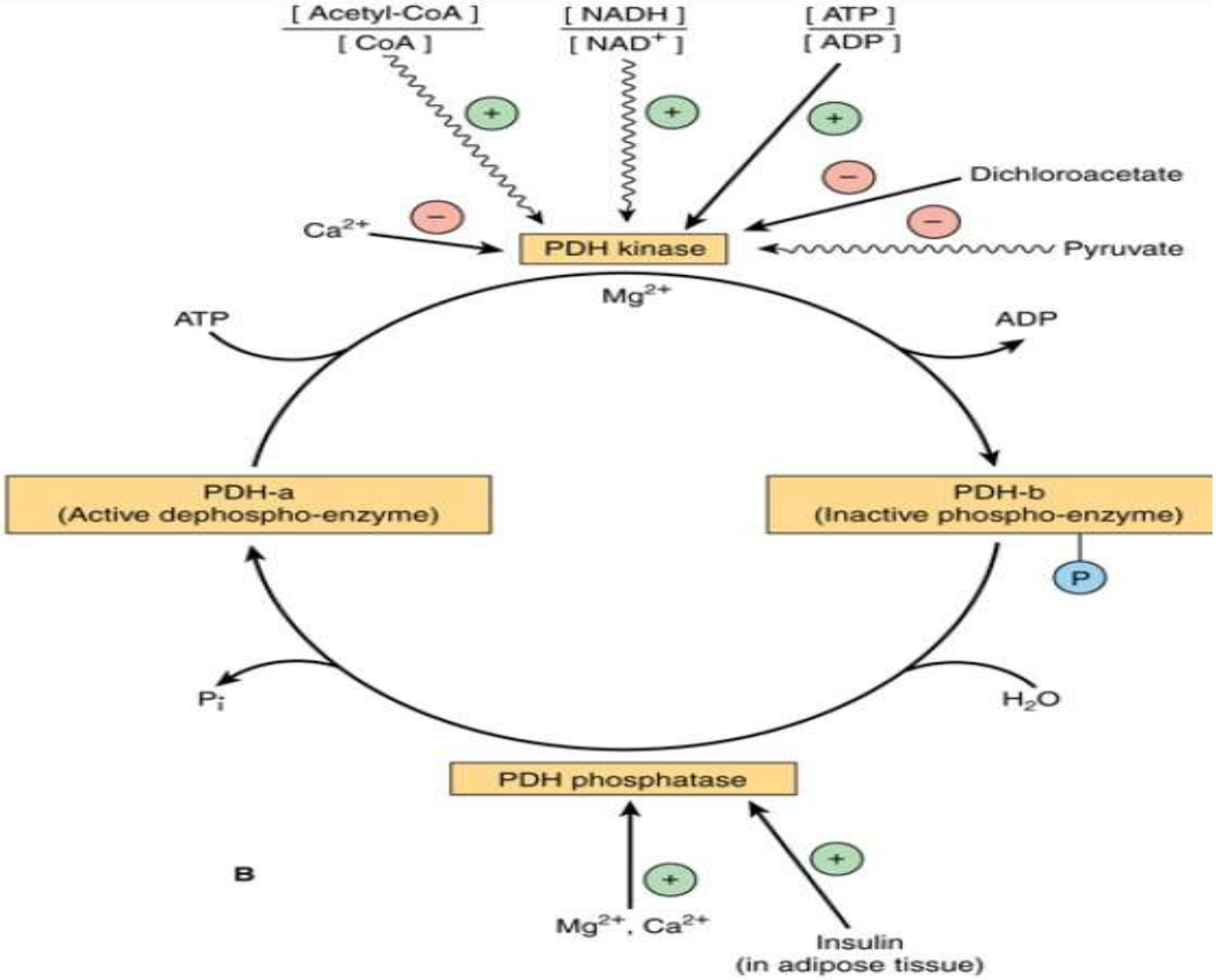


2. SHORT- & LONG-TERM MECHANISMS REGULATE LIPOGENESIS

3. Acetyl-CoA Carboxylase Is the Most Important Enzyme in the Regulation of Lipogenesis

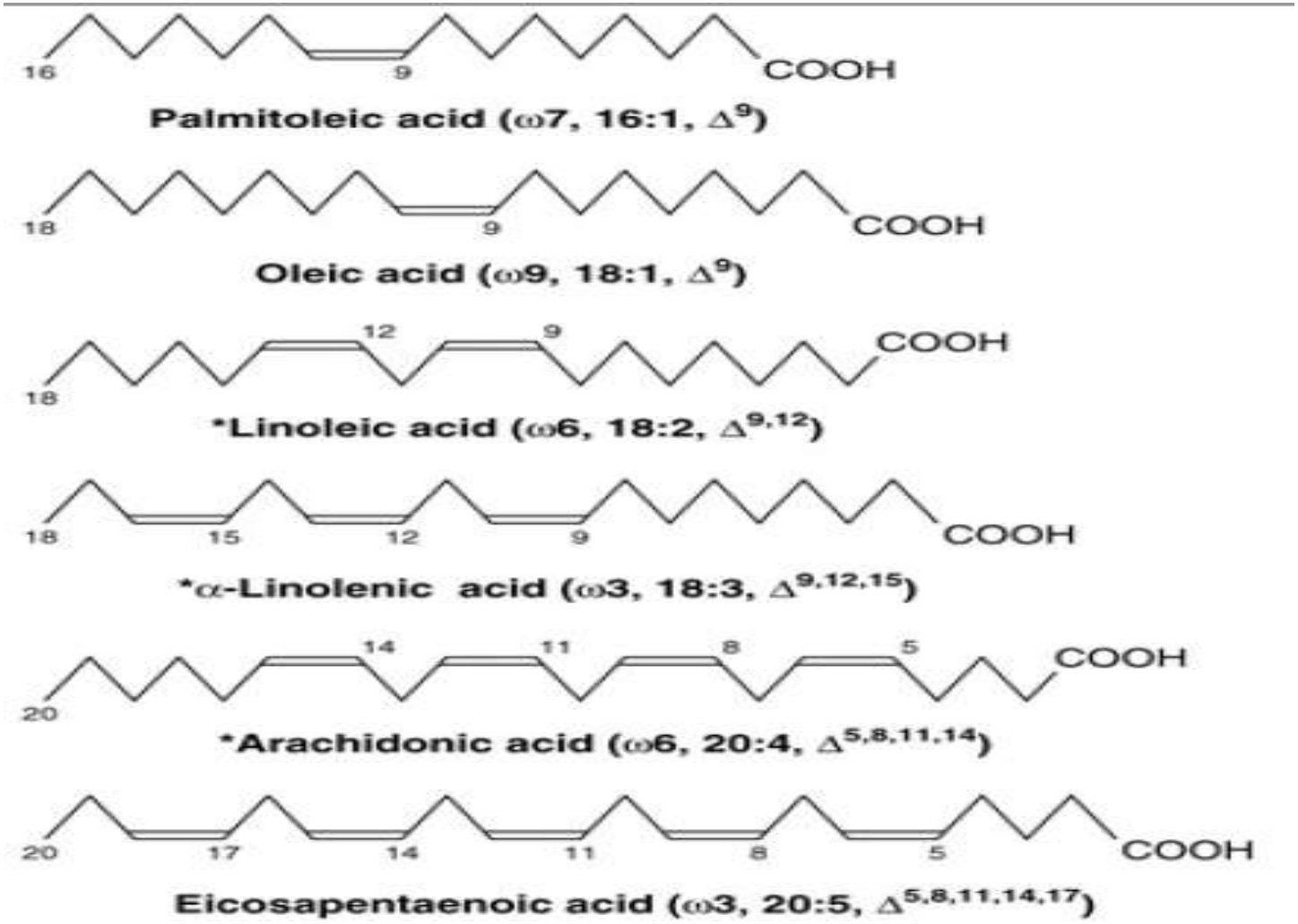


4. Pyruvate Dehydrogenase Is Also Regulated by Acyl-CoA

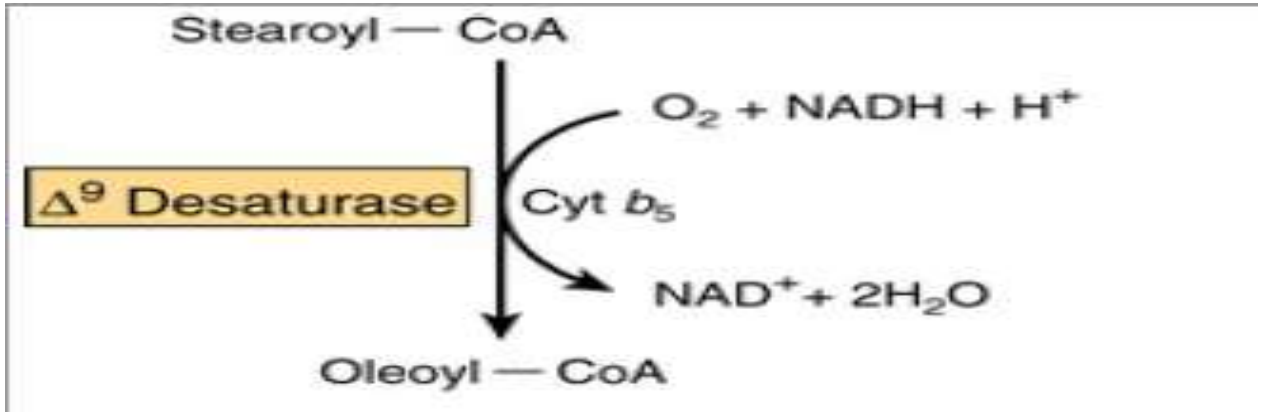


5. Insulin Also Regulates Lipogenesis by Other Mechanisms

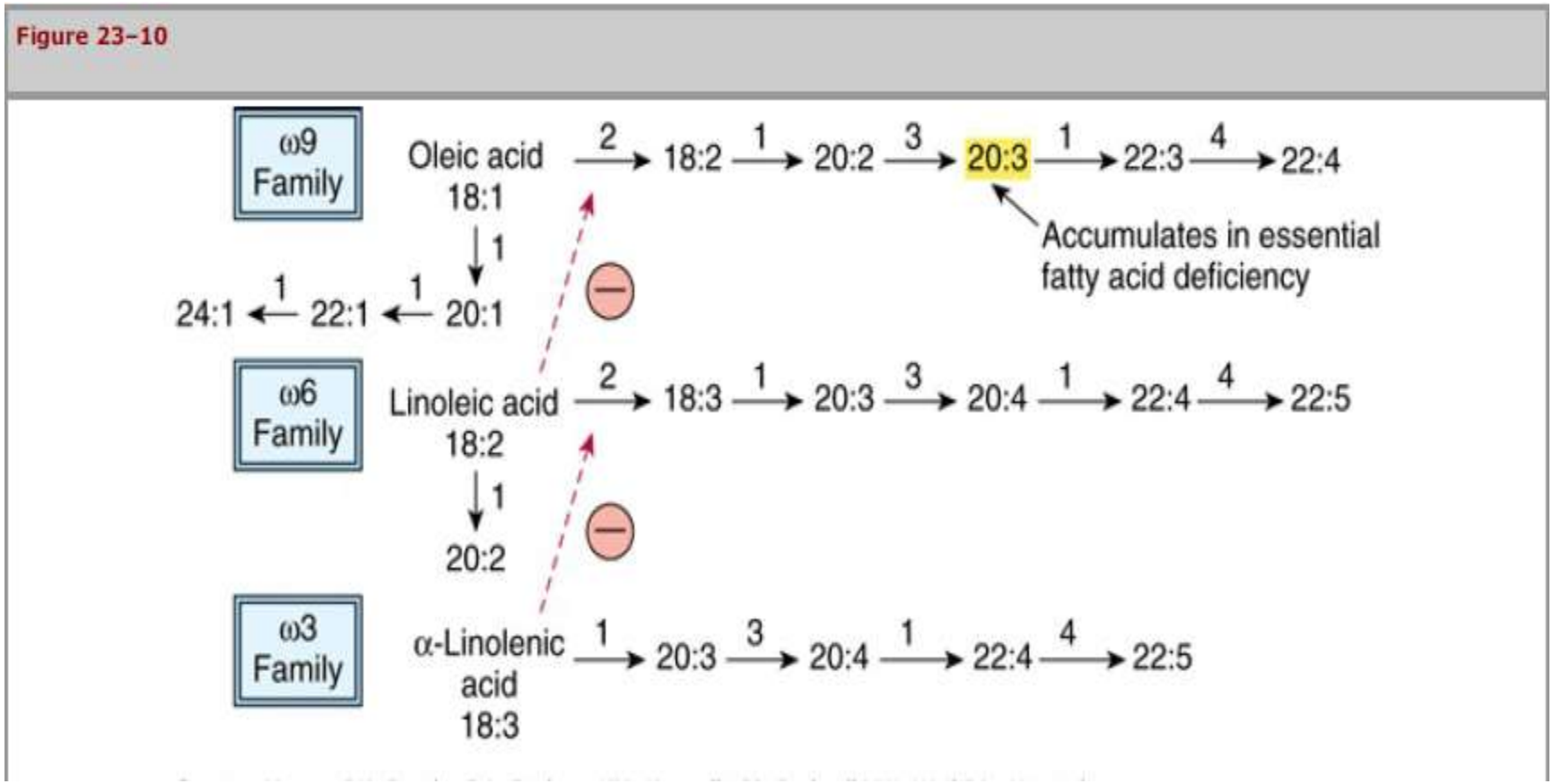
SOME POLYUNSATURATED FATTY ACIDS CANNOT BE SYNTHESIZED BY MAMMALS & ARE NUTRITIONALLY ESSENTIAL



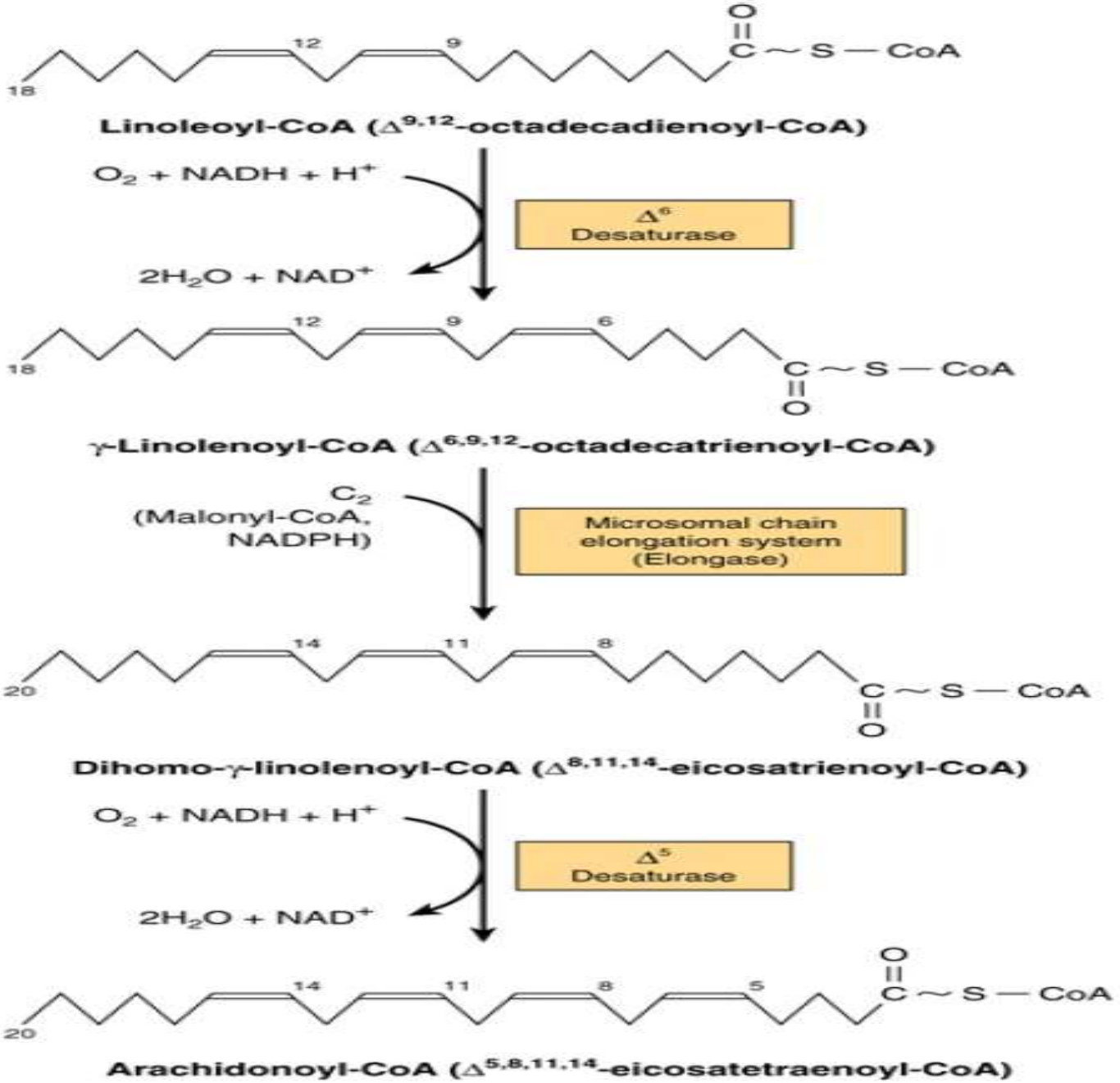
MONOUNSATURATED FATTY ACIDS ARE SYNTHESIZED BY A 9 DESATURASE SYSTEM



SYNTHESIS OF POLYUNSATURATED FATTY ACIDS INVOLVES DESATURASE & ELONGASE ENZYME SYSTEMS



1: elongase, **2:** Δ6 desaturase, **3:**Δ 5 desaturase, **4:** Δ4 desaturase


18
12
9
O
C ~ S — CoA
Linoleoyl-CoA (Δ9,12-octadecadienoyl-CoA)
O2 + NADH + H+
2H2O + NAD+
Δ6 Desaturase
18
12
9
6
C ~ S — CoA
O
γ-Linolenoyl-CoA (Δ6,9,12-octadecatrienoyl-CoA)
C2
(Malonyl-CoA, NADPH)
Microsomal chain elongation system (Elongase)
20
14
11
8
C ~ S — CoA
O
Dihomo-γ-linolenoyl-CoA (Δ8,11,14-eicosatrienoyl-CoA)
O2 + NADH + H+
2H2O + NAD+
Δ5 Desaturase
20
14
11
8
5
O
C ~ S — CoA
Arachidonoyl-CoA (Δ5,8,11,14-eicosatetraenoyl-CoA)

OXIDATION OF FATTY ACIDS: KETOGENESIS

Figure 22–1

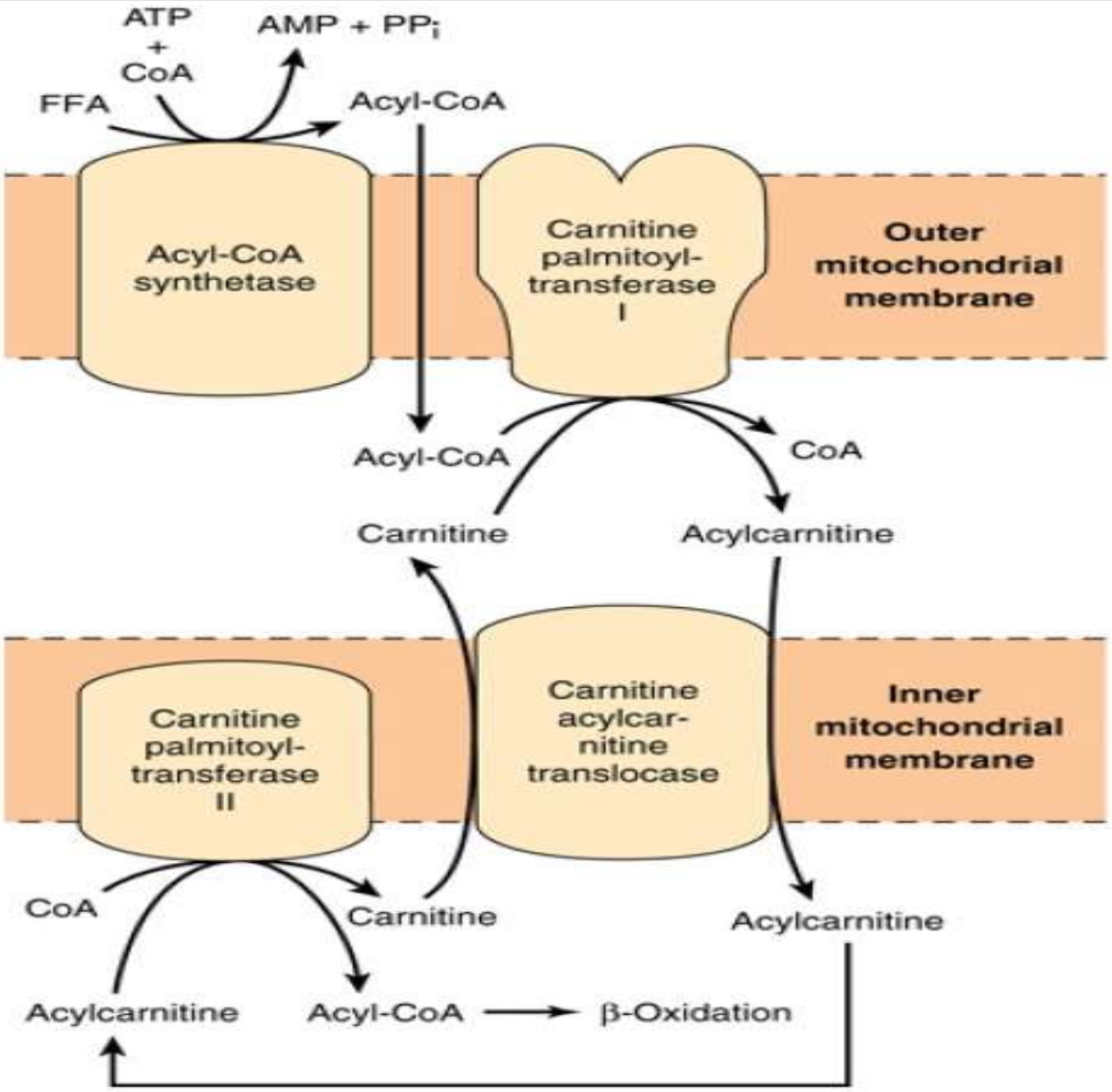
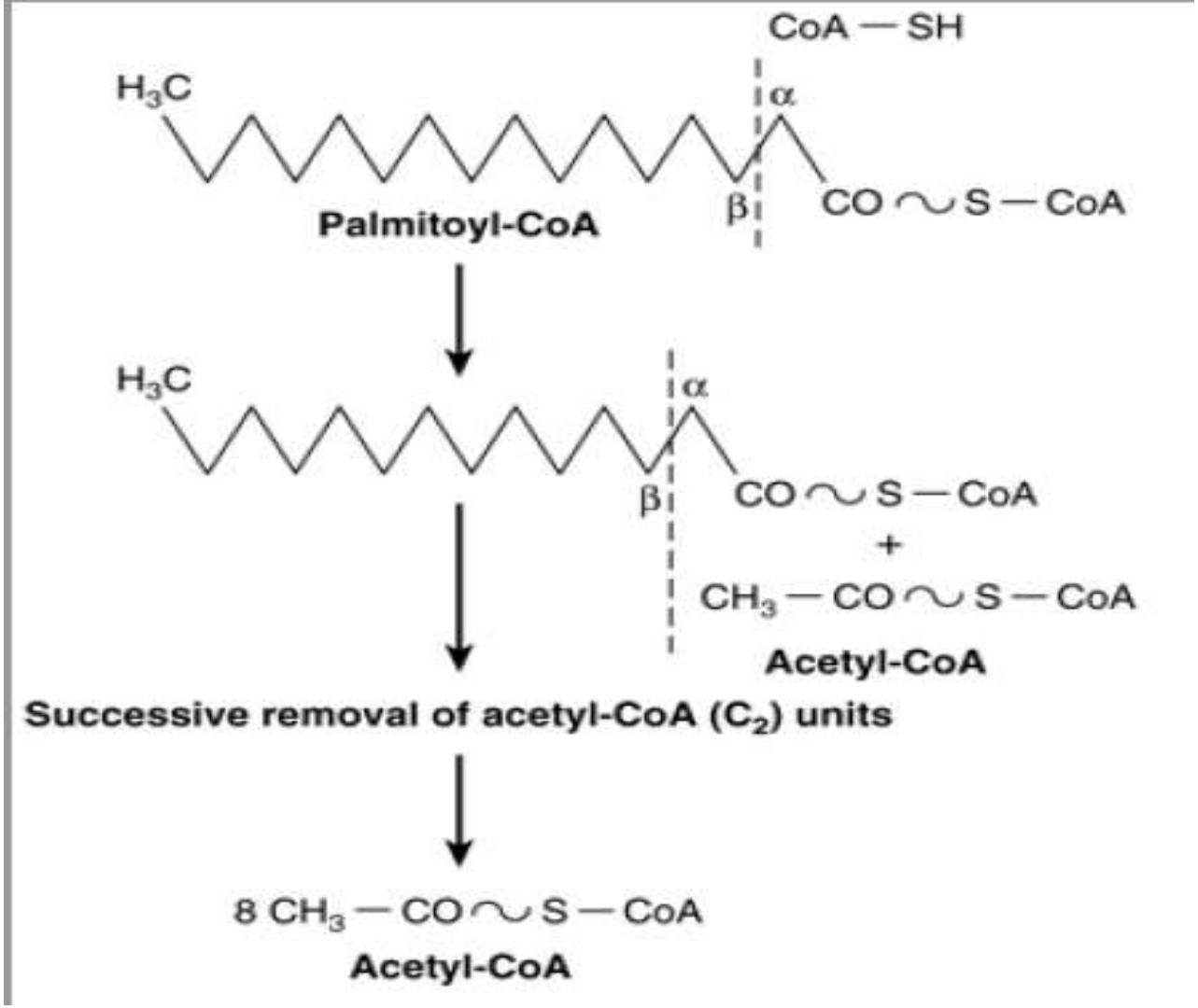
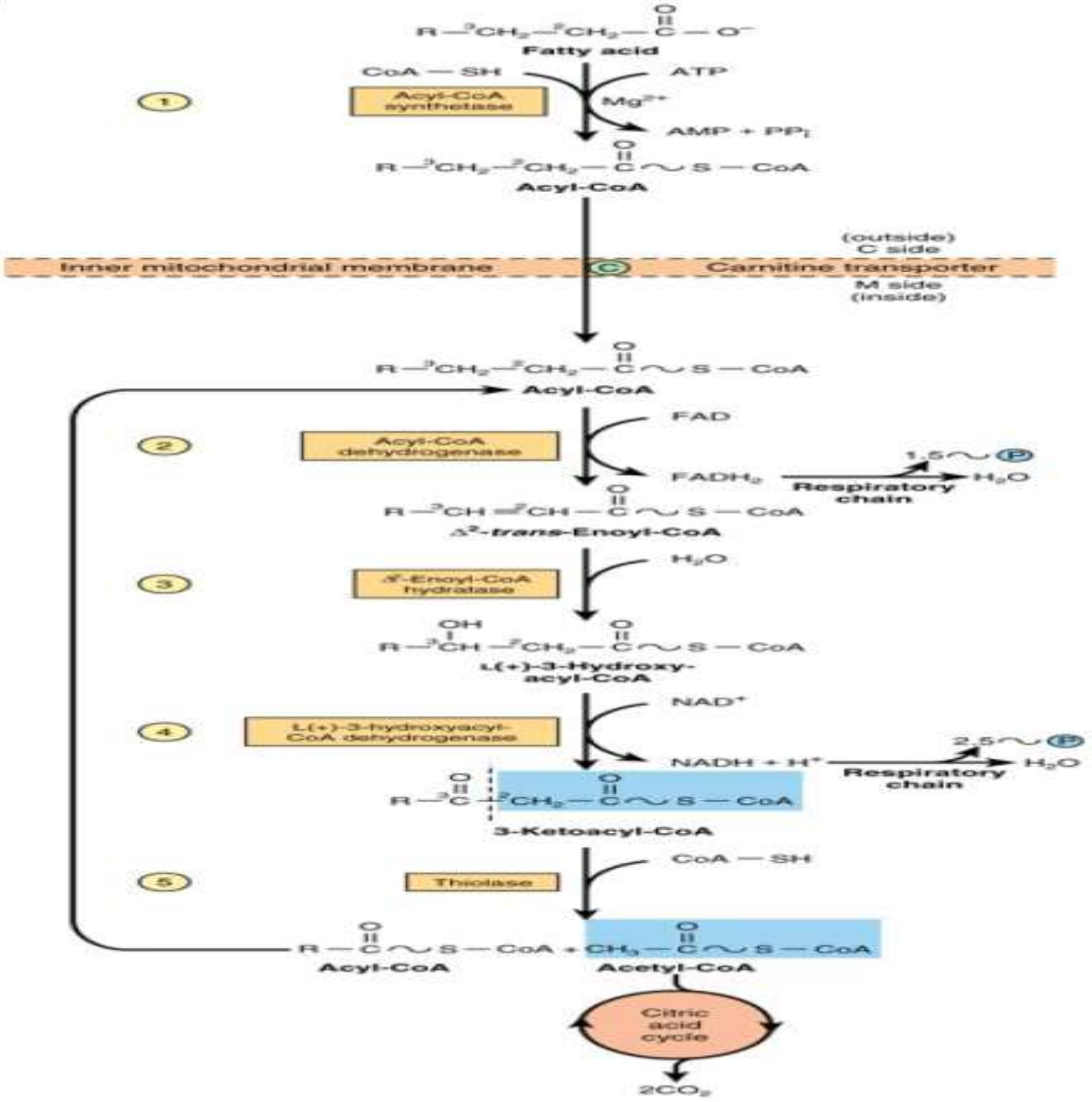
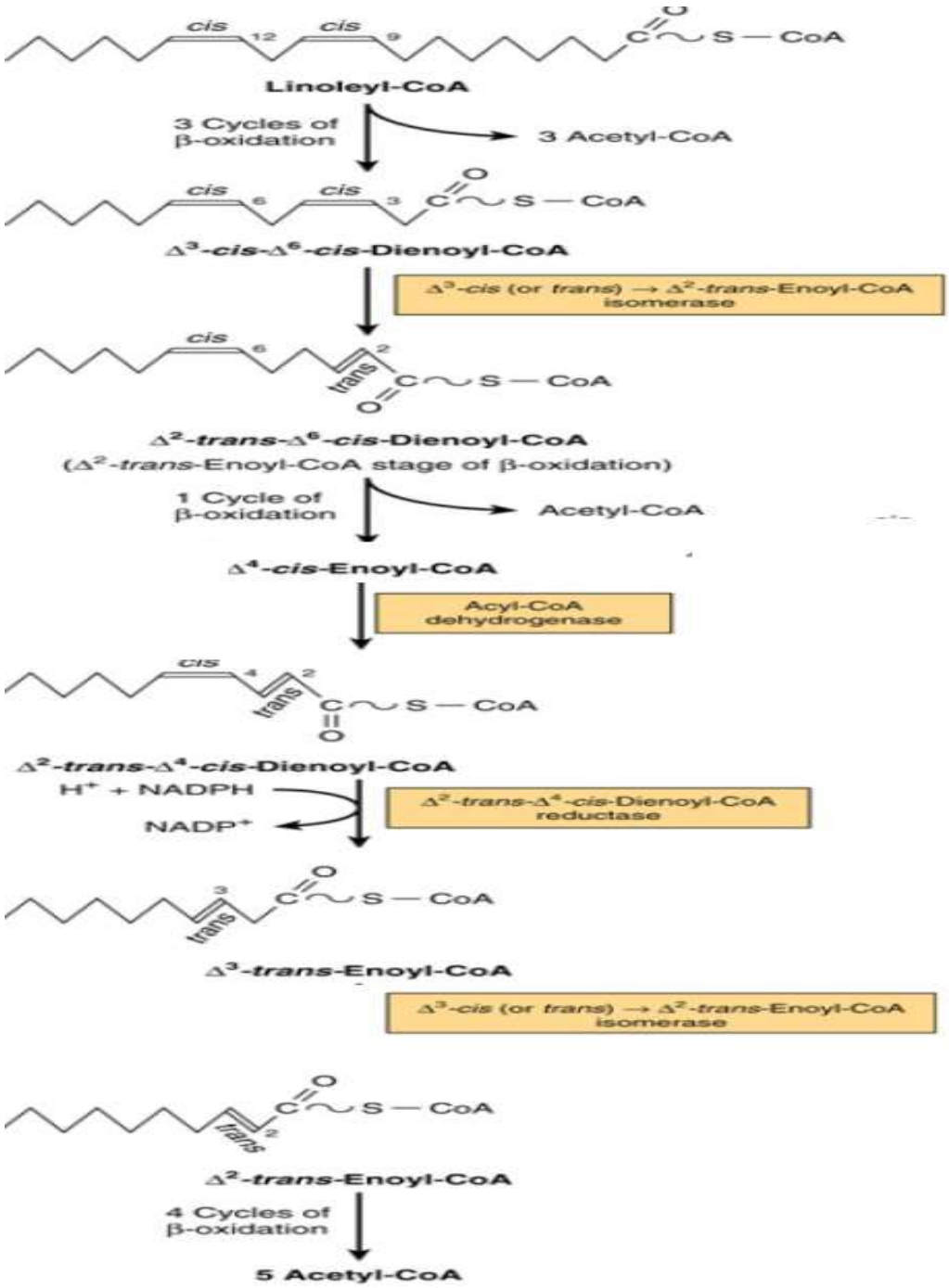


Figure 22–2

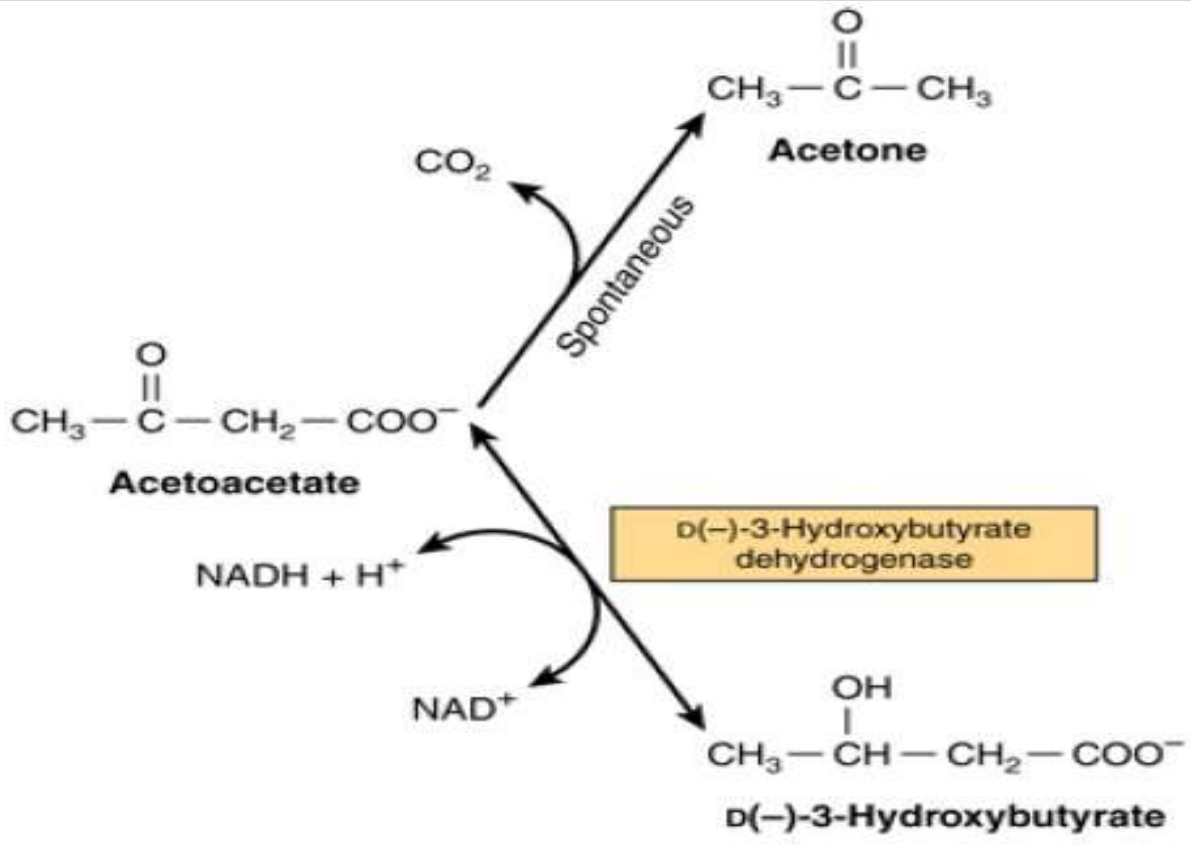

CoA — SH
H_3C
α
β
CO ~ S — CoA
Palmitoyl-CoA
H_3C
α
β
CO ~ S — CoA
+
CH_3 — CO ~ S — CoA
Acetyl-CoA
Successive removal of acetyl-CoA (C_2) units
8 CH_3 — CO ~ S — CoA
Acetyl-CoA

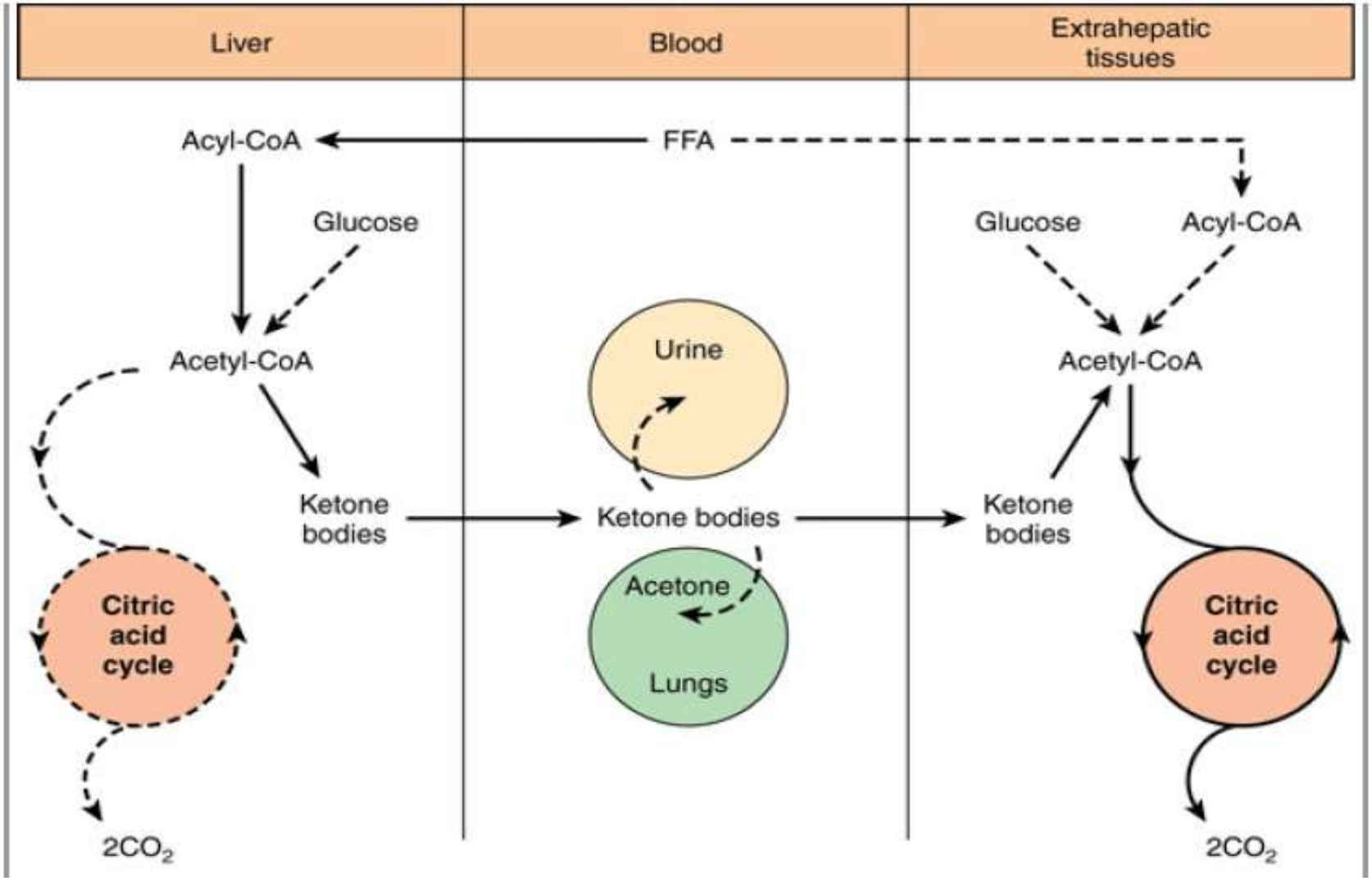

Fatty acid
CoA — SH
ATP
1
Acyl-CoA synthetase
Mg^{2+}
AMP + PP_i
Acyl-CoA
(outside)
C side
Inner mitochondrial membrane
C
Carnitine transporter
M side
(inside)
Acyl-CoA
2
Acyl-CoA dehydrogenase
FAD
$FADH_2$
1.5 ~ P
Respiratory chain
H_2O
Δ^2-trans-Enoyl-CoA
3
Δ^2-Enoyl-CoA hydratase
H_2O
L(+)-3-Hydroxy-acyl-CoA
4
L(+)-3-hydroxyacyl-CoA dehydrogenase
NAD^+
$NADH + H^+$
2.5 ~ P
Respiratory chain
H_2O
3-Ketoacyl-CoA
5
Thiolase
CoA — SH
Acyl-CoA
Acetyl-CoA
Citric acid cycle
$2CO_2$

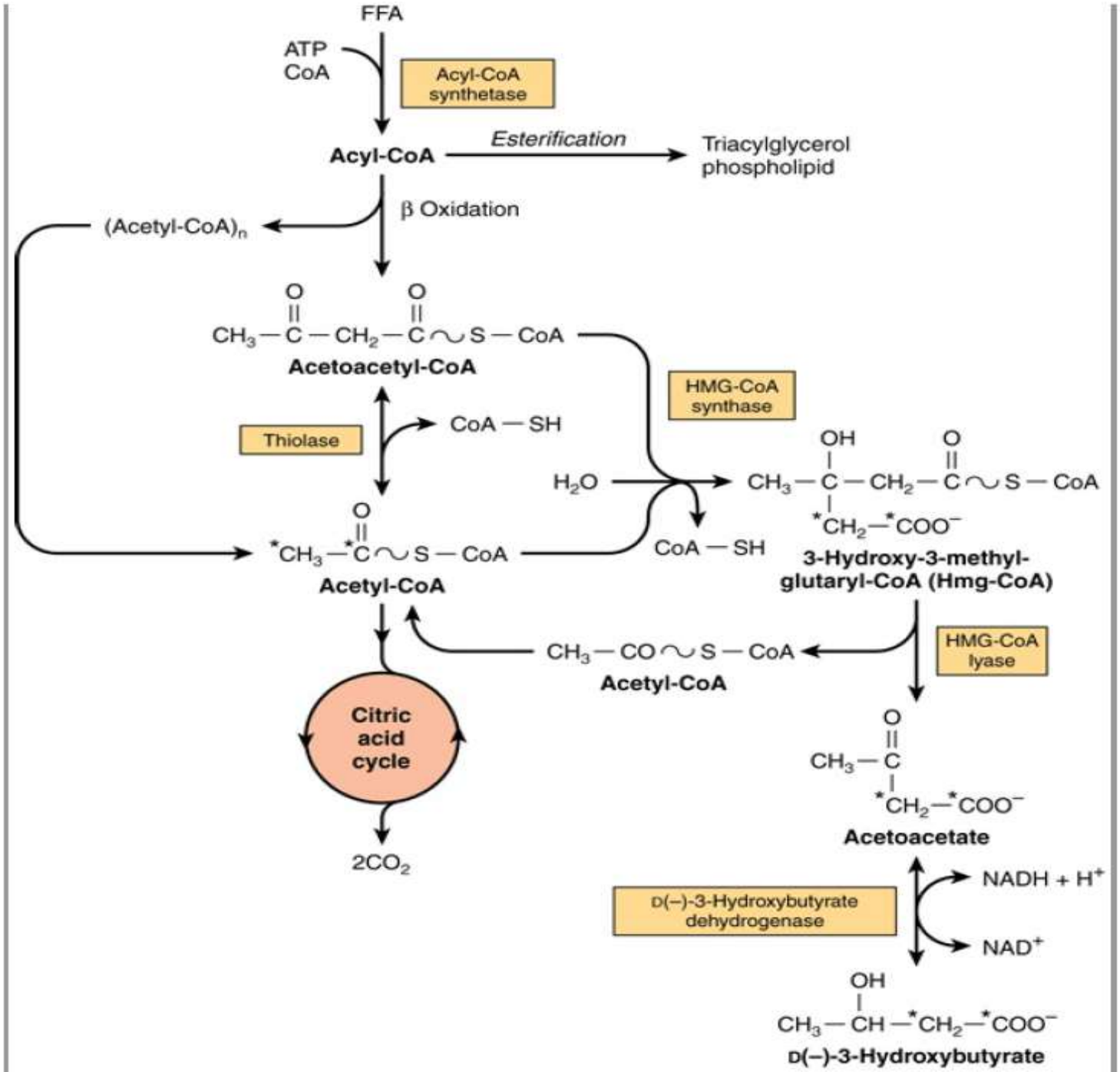

cis
12
cis
9
S — CoA
Linoleyl-CoA
3 Cycles of β-oxidation
3 Acetyl-CoA
cis
6
cis
3
S — CoA
Δ3-cis-Δ6-cis-Dienoyl-CoA
Δ3-cis (or trans) → Δ2-trans-Enoyl-CoA isomerase
cis
6
trans
2
S — CoA
Δ2-trans-Δ6-cis-Dienoyl-CoA
(Δ2-trans-Enoyl-CoA stage of β-oxidation)
1 Cycle of β-oxidation
Acetyl-CoA
Δ4-cis-Enoyl-CoA
Acyl-CoA dehydrogenase
cis
4
trans
2
S — CoA
Δ2-trans-Δ4-cis-Dienoyl-CoA
H+ + NADPH
NADP+
Δ2-trans-Δ4-cis-Dienoyl-CoA reductase
trans
3
S — CoA
Δ3-trans-Enoyl-CoA
Δ3-cis (or trans) → Δ2-trans-Enoyl-CoA isomerase
trans
2
S — CoA
Δ2-trans-Enoyl-CoA
4 Cycles of β-oxidation
5 Acetyl-CoA

OXIDATION OF FATTY ACIDS: KETOGENESIS

Figure 22–5


O
CH3 — C — CH3
Acetone
CO2
Spontaneous
O
CH3 — C — CH2 — COO−
Acetoacetate
D(−)-3-Hydroxybutyrate dehydrogenase
NADH + H+
NAD+
OH
CH3 — CH — CH2 — COO−
D(−)-3-Hydroxybutyrate


Liver
Blood
Extrahepatic tissues
Acyl-CoA
FFA
Glucose
Glucose
Acyl-CoA
Acetyl-CoA
Urine
Acetyl-CoA
Ketone bodies
Ketone bodies
Ketone bodies
Acetone
Lungs
Citric acid cycle
Citric acid cycle
2CO2
2CO2


FFA
ATP
CoA
Acyl-CoA synthetase
Acyl-CoA
Esterification
Triacylglycerol phospholipid
β Oxidation
(Acetyl-CoA)n
Acetoacetyl-CoA
HMG-CoA synthase
Thiolase
CoA — SH
H2O
CoA — SH
3-Hydroxy-3-methyl-glutaryl-CoA (Hmg-CoA)
Acetyl-CoA
CH3 — CO ~ S — CoA
Acetyl-CoA
HMG-CoA lyase
Citric acid cycle
2CO2
Acetoacetate
D(−)-3-Hydroxybutyrate dehydrogenase
NADH + H+
NAD+
D(−)-3-Hydroxybutyrate

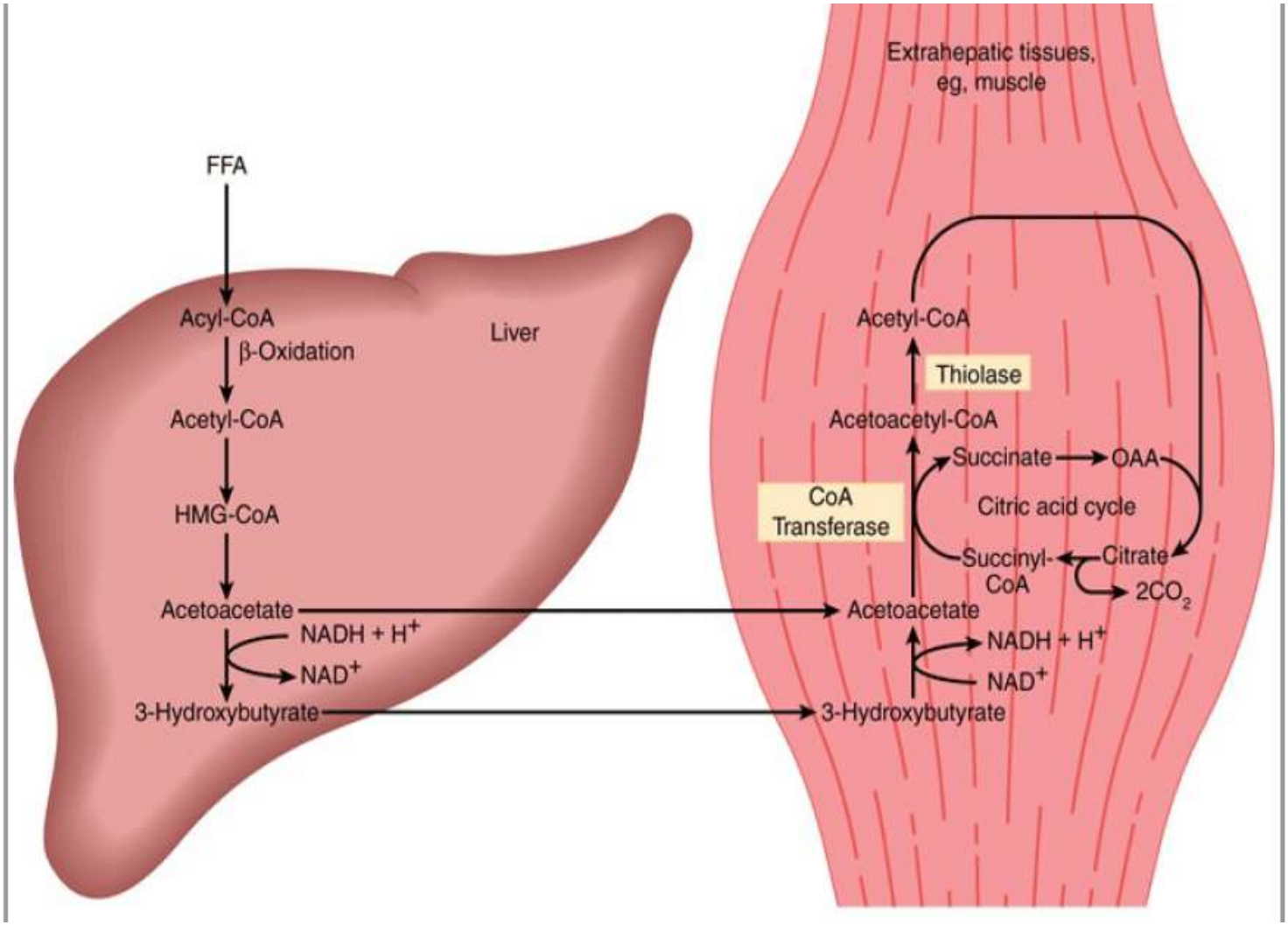
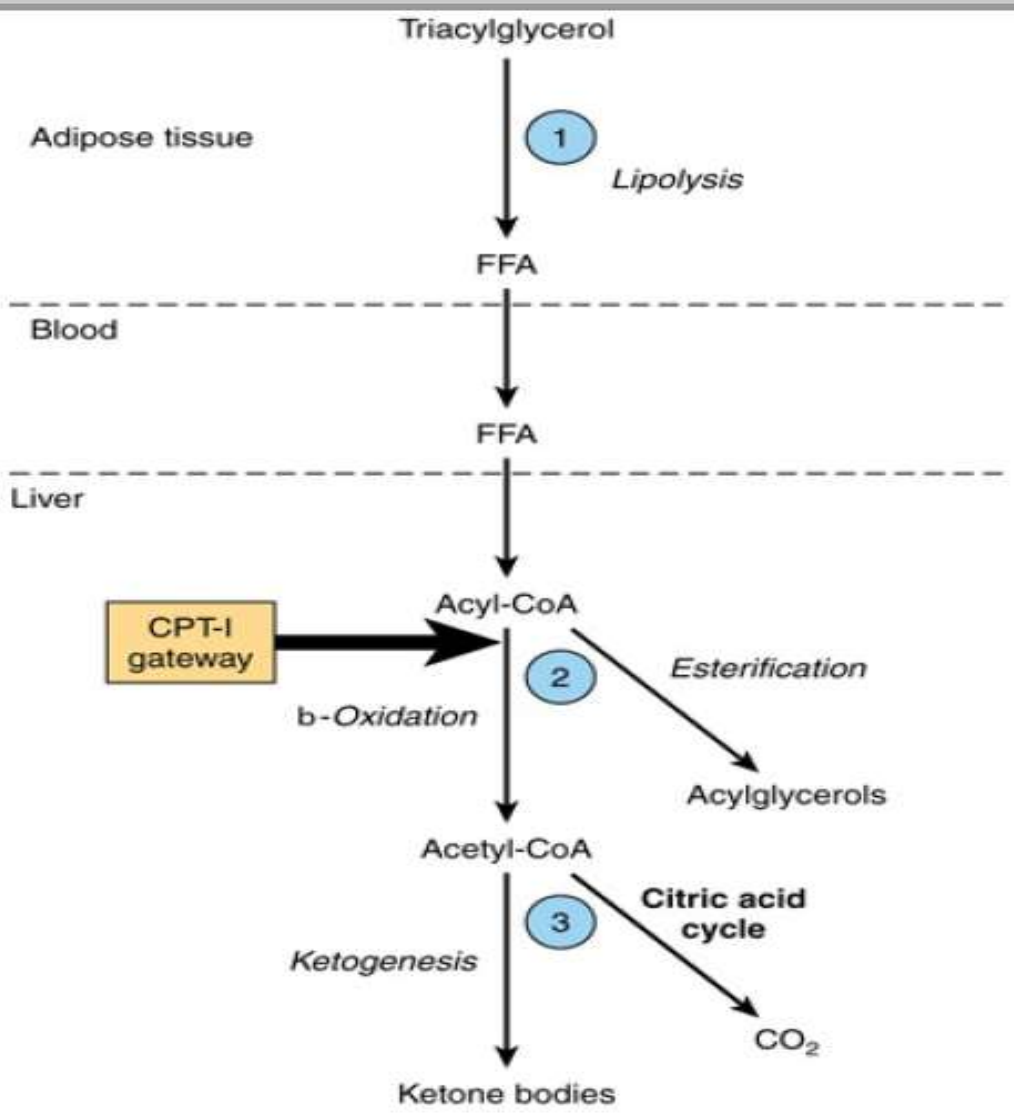
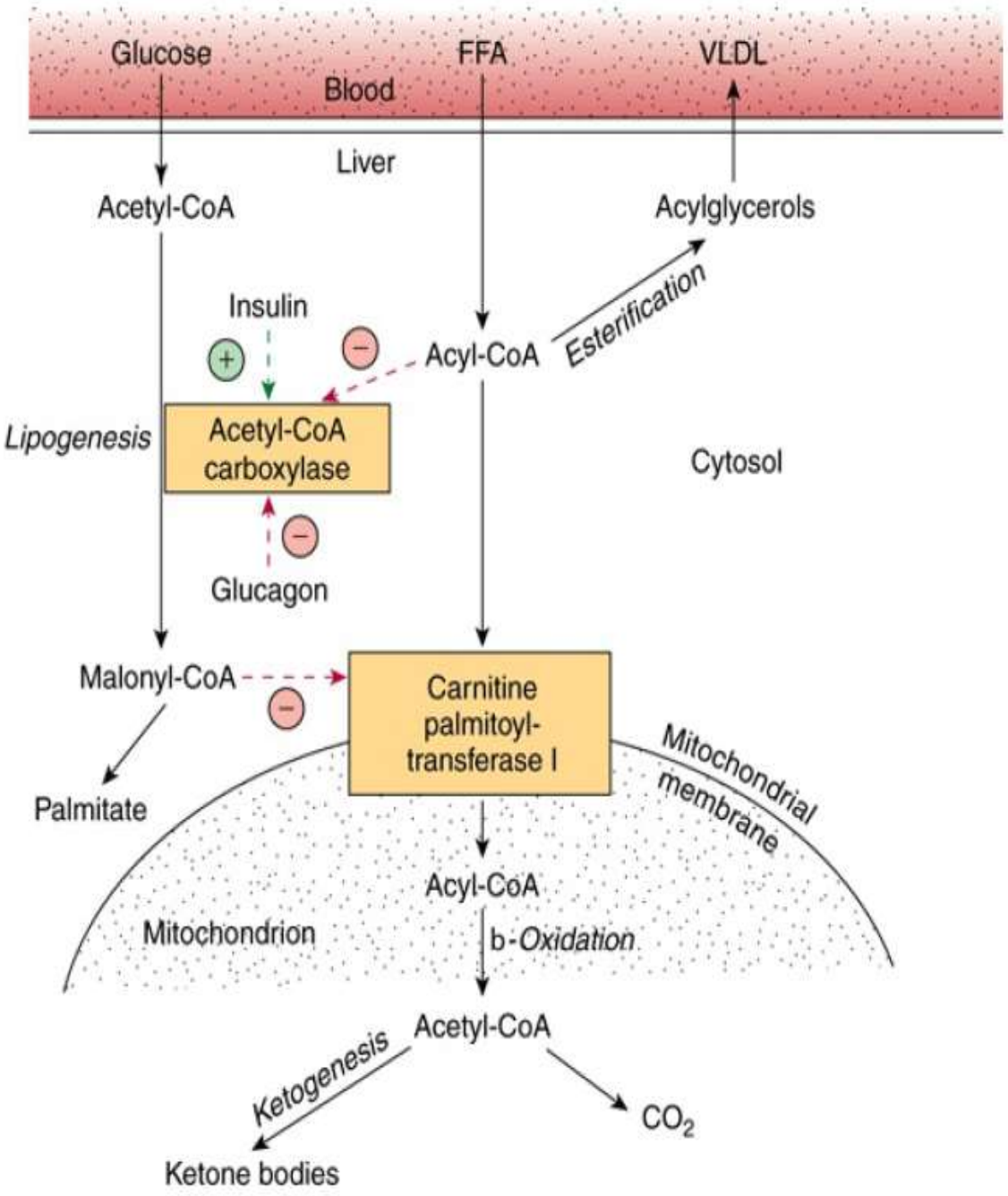

Extrahepatic tissues,
eg, muscle
FFA
Acyl-CoA
β-Oxidation
Acetyl-CoA
HMG-CoA
Acetoacetate
NADH + H+
NAD+
3-Hydroxybutyrate
Liver
Acetyl-CoA
Thiolase
Acetoacetyl-CoA
Succinate
OAA
CoA
Transferase
Citric acid cycle
Succinyl-
CoA
Citrate
2CO2
Acetoacetate
NADH + H+
NAD+
3-Hydroxybutyrate

Figure 22–9


Triacylglycerol
Adipose tissue
1
Lipolysis
FFA
Blood
FFA
Liver
Acyl-CoA
CPT-I gateway
2
Esterification
b-Oxidation
Acylglycerols
Acetyl-CoA
3
Citric acid cycle
Ketogenesis
CO_2
Ketone bodies


Glucose
Blood
FFA
VLDL
Liver
Acetyl-CoA
Acylglycerols
Insulin
Acyl-CoA
Esterification
Lipogenesis
Acetyl-CoA carboxylase
Cytosol
Glucagon
Malonyl-CoA
Carnitine palmitoyl-transferase I
Palmitate
Mitochondrial membrane
Acyl-CoA
Mitochondrion
b-Oxidation
Acetyl-CoA
Ketogenesis
CO_2
Ketone bodies